Archives of Neurology and Psychiatry

VOLUME 55 JANUARY 1946 NUMBER 1

HISTOPATHOLOGIC EFFECT OF ANOXIA ON THE CENTRAL NERVOUS SYSTEM

L. RAYMOND MORRISON, M.D.

BOSTON

Damage to the nervous system as a consequence of anoxia has been produced in many ways, but most of the investigations dealing with this subject have borne but slight relation to the problem of aviation. Illuminating and important as many of these previous clinical and experimental studies have been, they have not, with few exceptions, been concerned with precisely the conditions met with in aviation. The purpose of the present investigation was to determine whether histologic alterations were produced in the central nervous system after repeated, sublethal exposures to an atmosphere deficient in oxygen; to measure the amount of oxygen to which the nervous system was exposed, and to correlate that amount, if possible, with the nature of the histologic process. The extensive use of the high flying airplane in war, with its accompanying hazards of failure of oxygen supply, jumps from high altitudes and the possible cumulative effect of the chronic day by day exposure to fatigue and anoxia, makes the need for such an investigation imperative. It is well known [1] that acute and chronic altitude sickness was a major problem in the first world war and in commercial aviation after the war; and while greatly improved precautionary measures are in use at the present time, the possibility of neurogenic deterioration among pilots and other fliers has in no sense been eliminated.[2] An attempt has been made, therefore, to investigate the effect on the brain of repeated exposures to degrees of anoxia which in a single exposure would have but transient effect.

The different conditions under which anoxia of the nervous system has been produced may be grouped under the classification of anoxias as suggested by Barcroft,[3] or by Peters and Van Slyke.[4] 1. Anoxic anoxia is characterized by low oxygen tension of the arterial blood, so that the hemoglobin does not have its normal degree of oxygen saturation. 2. Anemic anoxia is a condition in which insufficient amounts of hemoglobin are available for oxygen transport even though the oxygen tension is normal. 3. Stagnant anoxia is the result of defective circulation of blood during which the tissues fail to receive an adequate supply of oxygen even though the arterial blood contains sufficient oxygen in the proper degree of saturation. 4. Histotoxic anoxia occurs when the tissue cells themselves are unable to utilize oxygen even though it is available in the arterial blood.

As a frame of reference this classification has a good deal of practical value. Since the methods of producing the various kinds of anoxia differ from one another, the local physiologic effects on the brain are not exactly the same, and, consequently, the resulting pathologic lesions show certain variations with the different types of anoxia. While it is not always possible to identify the type of anoxia from the nature of the neuropathologic lesion, there are certain characteristic features that are of value. Without anticipating the results of this experiment, it may be pointed out, for example, that zones of laminar cortical necrosis were found in a monkey that had been subjected to anoxic anoxia in a decompression chamber and these lesions were apparently identical with those reported by Courville [5] in cases of anoxic anoxia incident to nitrous oxide anesthesia. On the other hand,

From the Department of Neuropathology, Harvard Medical School, and the Neuropathology Laboratory, Massachusetts General Hospital.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the office of Scientific Research and Development and Harvard University.

1. Armstrong, H. G.: Anoxia in Aviation, J. Aviation Med. **9**:84, 1938.

2. Jokl, E.: Medical Problems of Aviation, J. Roy. Army M. Corps **73**:289, 1939.

3. Barcroft, J.: Anoxemia, Lancet **2**:485, 1920.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 1264.

5. Courville, C. B.: Asphyxia Following Nitrous Oxide Anesthesia, Medicine **15**: 129, 1936.

it should also be pointed out that a case can likewise be built up for the fact that certain overlapping similarities in the pathologic picture of the different types of anoxia do occur, depending, at least in part, on the intensity of the exposure, the cumulative effect and the duration of the survival. While it is difficult to compare the lesions of acute stagnant anoxia following vascular occlusion, such as those reported by Gildea and Cobb,[6] with the early lesions of anemic anoxia produced by inhalation of carbon monoxide[7] because of the difference in time during which the anoxia was effective, it is nevertheless true that shrunken and deeply stained nerve cells were the changes first seen with both types of anoxia. Other similarities will be discussed later.

There is an extensive literature covering the effects of all these types of anoxia on the central nervous system, a critical review of which will be entirely omitted from this paper. The interested reader can readily orient himself by consulting a few key references to the various types of anoxia. For information on stagnant anoxia, ligature type, de Buck and de Moor,[8] Gildea and Cobb,[6] Tureen[9] and Weinberger and the Gibbons[10] may be consulted. Anemic anoxia, inhalation type, has been covered by Ruge,[11] Ferraro and Morrison,[7] Sayers and Davenport[12] and many others. Histotoxic anoxia has been well studied by Ferraro[13] and by Hurst,[14] while information on the effects of anoxic anoxia on the central nervous system has been reviewed and added to by Courville,[5] Armstrong and Heim,[15] Thorner and Lewy[16] and others. The observations of these and other investigators will be referred to when necessary, but, for the sake of brevity, their work will not be discussed at this time.

MATERIALS AND METHODS

An air-tight chamber made of steel and glass, modeled after the one used by Hastings and associates,[17] was used as a gassing compartment for some of the animals. Air was mixed with nitrogen through the medium of an oxygen concentration meter[18] and introduced into the chamber. Carbon dioxide was removed from the chamber atmosphere by circulating the chamber gas through a soda lime tower. It was attempted to cool the chamber atmosphere by passing the circulating gas through a copper coil immersed in ice water. Samples of the gas mixture for analysis were obtained from the chamber atmosphere. The hindquarters of the dog were drawn through an air-tight rubber sleeve in one side of the chamber, so that blood could be obtained from the femoral artery.

Most of the animals, however, were given the gas mixture by means of a mask. This was found satisfactory after a brief preliminary training. The dog was secured in a recumbent position to an animal operating table, and an air-tight gas mask was strapped over his mouth and nose. The mask was made of heavy celluloid and was made air tight in relation to the dog's head by means of an air-inflated rubber cushion. The mask was equipped with one inlet and one outlet unidirectional valve. Air was mixed with nitrogen through the same kind of oxygen concentration meter as that used with the chamber. Samples of the air-nitrogen mixture were taken for analysis from a collecting bag attached to the gas mask. There was no rebreathing, for the outlet valve had no egress to the collecting bag; so carbon dioxide did not accumulate. Blood was obtained from the femoral artery. The oxygen and carbon dioxide contents of the gas mixture were determined by the method of Haldane[19] and those of the blood by the method of Van Slyke.[20] Hematocrit readings were usually made, and on certain occasions determinations of sugar content were carried out.

Twenty-five dogs were exposed to such atmospheres deficient in oxygen. The exposures were usually made

6. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

7. Ferraro, A., and Morrison, L. R.: Illuminating Gas Poisoning: An Experimental Study of the Lesions of the Nervous System in Acute and Chronic Stages, Psychiatric Quart. **2**:506, 1928.

8. de Buck, D., and de Moor, L.: Lésions des cellules nerveuses sous l'influence de l'anémie aiguë, Névraxe **2**:2, 1900-1901.

9. Tureen, L. L.: Circulation of the Spinal Cord and the Effect of Vascular Occlusion, A. Research Nerv. & Ment. Dis., Proc. **18**:394, 1938.

10. Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation of the Central Nervous System, Arch. Neurol. & Psychiat. **43**: 615 (April) 1940.

11. Ruge, A.: Kasuistscher Beitrag zur pathologischen Linsenkernerweichung bei CO Vergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **64**:45, 1922.

12. Sayers, R. R., and Davenport, S. J.: Review of Carbon-Monoxide Poisoning, Public Health Bulletin 195, United States Treasury Department, Public Health Service, 1930.

13. Ferraro, A.: Experimental Toxic Encephalomyelopathy: Diffuse Sclerosis Following Subcutaneous Injection of Potassium Cyanide, Psychiatric Quart. **7**: 267, 1933.

14. Hurst, E. W.: Experimental Demyelination of the Central Nervous System, Australian J. Exper. Biol. & M. Sc. **18**:201, 1940; **20**:297, 1942.

15. Armstrong, H. G., and Heim, J. W.: Effect of Repeated Daily Exposures to Anoxemia, J. Aviation Med. **9**:92, 1938.

16. Thorner, M. W., and Lewy, F. H.: The Effects of Repeated Anoxia on the Brain, J. A. M. A. **115**: 1595 (Nov. 9) 1940.

17. Cohen, D. J.; Tannenbaum, A.; Thalhimer, W., and Hastings, A. B.: Influence of Oxygen and Carbon Dioxide on the Blood of Normal and Pneumonic Dogs, J. Biol. Chem. **128**:109, 1939.

18. Barach, A. L., and Eckman, M.: A Mask Apparatus Which Provides High Oxygen Concentrations with Accurate Control of the Percentage of Oxygen in the Inspired Air and Without Accumulation of Carbon Dioxide, J. Aviation Med. **12**:39, 1941.

19. Peters and Van Slyke,[4] 1932, vol. 2, p. 981.

20. Horvath, S. M.; Consolazio, W. V., and Dill, D. B.: Syllabus of Methods of the Fatigue Laboratory of Harvard Business School, Harvard University, Cambridge, Mass., 1942.

daily, except Sundays, were three to four hours in length and varied in number from 1 to 40. The oxygen content of the atmospheres ranged from 13 to about 4.5 per cent. The atmosphere inspired was always at normal pressure.

In addition to these dogs, the brains and spinal cords of 10 monkeys were studied. These monkeys had been subjected, from 1 to 114 times, to daily anoxia in a decompression chamber. Practically all the animals had been sent to a simulated altitude of 30,000 feet (9,000 meters), equivalent to a pressure of 225 mm. of mercury, or an oxygen content of ± 6 per cent.

One of the monkeys and 5 of the dogs were killed with ether. All the other animals that did not die at altitude were killed by intravenous injection of pentobarbital sodium.

The monkey brains and a few of the dog brains were fixed in toto. Most of the dog brains, however, were blocked at autopsy, and pieces were placed in various fixatives, those most commonly used being solution of formaldehyde U. S. P. diluted 1 to 10, 95 per cent alcohol, absolute alcohol and solution of formaldehyde U. S. P.-bromide and solution of formaldehyde U. S. P.–urea–potassium iodide fixatives. The stains employed in varying degrees with the different animals were: cresyl violet; hematoxylin and eosin; oil red O, and the Weigert–Van Gieson, Spielmeyer (or Weigert or Weil), Bielschowsky (or Bodian), Dockrill (oligodendroglia), Hortega (microglia), Cajal gold chloride-mercury bichloride, Holzer, Perdrau and Best carmine (glycogen) methods. Occasionally the Eros, Pickworth or Alzheimer–Mann method was used.

Blocks were taken from the frontal, parietal, temporal and occipital lobes and from the cerebellum, pons and medulla. Usually sections of the whole brain were made from blocks cut according to Meynert's method at the level of the anterior and the posterior end of the hypothalamus, at about planes X and XV in the atlas of Winkler and Potter.[21] A few spinal cords were likewise examined, both from dogs and monkeys. The splanchnic nerve was also studied. In addition, the adrenal glands were examined after being stained with the oil red O and the phenylhydrazine method.[22]

The brains of 5 normal dogs and of 2 normal monkeys were prepared by the same technics as those used in the experiment, and these served as controls.

PATHOLOGIC EXAMINATION

The brains of 25 dogs and 10 monkeys were examined. The dogs had been exposed to low oxygen concentrations at normal, Boston atmospheric pressure, as previously described. Ordinarily, an animal received a three to four hour exposure daily. The monkeys were likewise exposed daily, but a decompression chamber was used, so that low pressure atmospheric oxygen produced the pathologic effect. Since the lesions in the monkey brains were, to a certain extent, an accentuation of those found in the dog brains, the latter will be considered first.

21. Winkler, C., and Potter, A.: An Anatomical Guide to Experimental Researches on the Cat's Brain, Amsterdam, W. Versluys, 1914.

22. Bennett, H. S.: The Life History and Secretion of the Cells of the Adrenal Cortex of the Cat, Am. J. Anat. **67**:151, 1940.

DOGS

GROSS INSPECTION

Most of the dog brains presented no macroscopic abnormalities; they were not unusually injected, although the brain of 1 animal (Sophy) was strikingly pale, nor did they bulge or feel tense when the dura was opened. Mild, fresh hemorrhage was sometimes observed over the base, but this almost invariably proved later to be unaccompanied with any reaction and occurred probably post mortem. On section also there was but little abnormal to be seen. The small hemorrhages so often reported with anoxia [23] were virtually never present. On palpation, occasional small foci of softening were to be felt in the basal ganglia, usually bilaterally; and occasionally also in the subcortical white matter, particularly in the centrum semiovale, there were small, gray, rough patches. These were not nearly so common in the dogs as they were in the monkeys, as will be described later.

MICROSCOPIC EXAMINATION

The alterations that occurred in the brains may be roughly divided into two categories: lesions in the gray matter and lesions in the white matter. Each of these may be further subdivided into lesions of type 1 and lesions of type 2. The chief purpose in thus subdividing the histologic reactions encountered is convenience in description, although it is also true that certain of the reactions were characteristic in their location and type.

Lesions of Gray Matter: Type 1.—What has been called the first type of lesion in the gray matter is really a combination of at least two types of changes in the nerve cells, together with whatever concomitant interstitial reaction there was. These alterations have been grouped under one heading because they were the earliest and most consistent response which the brain made to this type of anoxia and because they were probably also, as will be pointed out later, at least partially reversible. With the Nissl stain, the ganglion cells of the outer cortical layers were usually pale, chromatolytic, swollen and vacuolated. These phenomena varied from one animal to another and sometimes from one region of the brain to another in the same animal. The cells sometimes showed more swelling, chromatolysis and related changes than at other times, but the same type of response was found in practically all the brains, as can be seen in table 1. These ganglion cells were usually convex in outline (fig. 1), with the nucleus eccentrically placed. The cytoplasm was pale and contained a number of vacuoles, the interstices

23. Armstrong and Heim.[15] Thorner and Lewy.[16]

of which were colored by a fine, dusty, pulverized tigroid substance. Sometimes these vacuoles were large, and three or four of them filled most of the perikaryon. Often, however, they were much smaller, and fifteen or twenty of them could be seen in the section of one cell. Usually, when the vacuoles were small the cell was rather dark, and when they were large the cell was pale. This vacuolation often extended out into the dendrites, as can be seen in figure 2, which shows a cell and its processes impregnated with silver. Often the nucleus and the perikaryon

TABLE 1.—*Data on Dogs Exposed to Atmospheres Deficient in Oxygen*

Dog	Number of Experiments	Number of Days	Oxygen in Blood, Vol. %	Lesion			
				Gray Matter Type 1	Gray Matter Type 2	White Matter Type 1	White Matter Type 2
Judith	25	33	13	+	..	..	..
Duncan	33	44	12	+	..	..	..
Pansy	10	11	11	+	..	..	..
Lillian	28	38	10	+	..	..	..
White Devil	29	60	10	+	..	..	..
Snowball	5	8	9	+	..	..	..
Casper	12	16	9	+	+	+	+
Allegra	44	61	8	+	..	+	..
Oscar	4	8	8	..	..	..	..
Horace	23	29	8	+	?	..	..
Sadie	19	31	7	+	..	+	+
Timothy	16	20	6	+	..	+	+
Edwin	13	15	5.5	+	..	..	+
Patricia	53	71	5	+	..	..	..
Harry	23	29	5	+	?	..	..
Hector	15	23	5	+	+	+	+
Sophy	12	18	5	+	..	..	+
Wiener	7	11	5	+	+	..	..
Tuck	39	52	4.5	+	..	+	+
Terry	35	43	4.5	+	..	+	+
Flora	33	42	4.5	+	+	..	..
Genevieve	33	43	4.5	+	..	..	..
Peter	12	45	4.5	+	+	+	+
Victor	11	22	4.5	+	+	..	+
Suzy	1	1	2.4	..	..	..	..

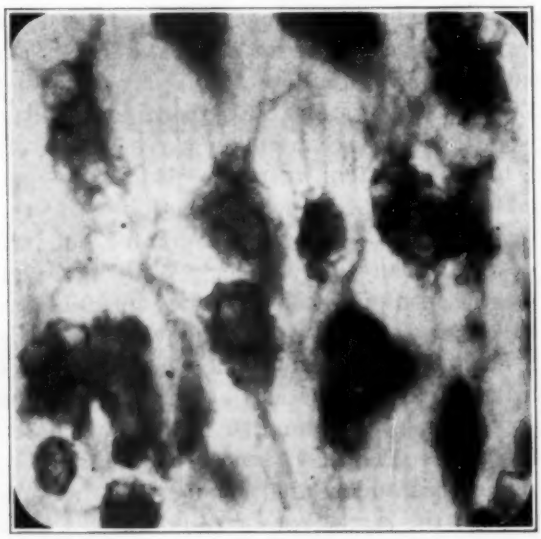

Fig. 1 (dog Sophy).—Liquefaction necrosis in the outer cortical layers. Nissl stain; × 400.

close to the nucleus appeared relatively normal, while the vacuoles around the outer margin of cytoplasm gave a fringed appearance to the edge of the cell. The glial nuclei in the same regions were reduced in number, and the cytoplasm of the oligodendroglia cells and the astrocytes was vacuolated, as it was in the nerve cells. In the Bielschowsky preparations, the neurofibrils passing through the perikaryon of these swollen, vacuolated cells were clumped and matted together and compressed to one side, or they extended like a cable through the depths of the cell close to the nucleus. Usually they took the stain poorly and gave a stippled appearance. In spite of the poor condition of the bodies of these swollen cells, the neurofibrils in the dendrites, especially in the apical dendrite, were well preserved.

In sections stained with oil red O for fat no fatty degeneration was obvious, but often after great care in adjusting the illumination a fine, dusty, pink powder could be made out within the vacuoles.

In addition to these cells of the supragranular layers in various parts of the cortex, the Purkinje cells exhibited swelling and vacuolation.

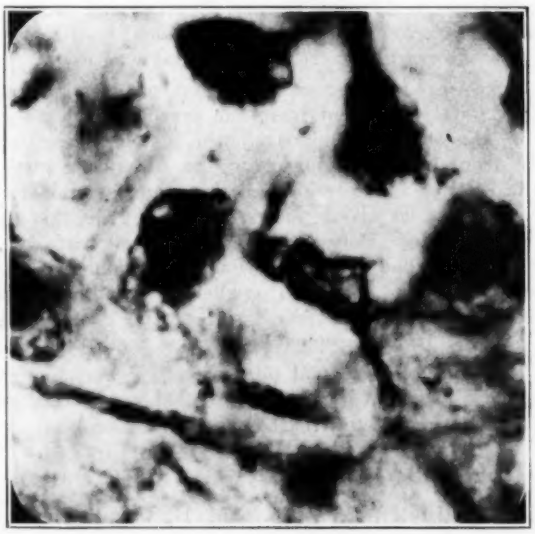

Fig. 2 (dog Wiener).—Swelling and vacuolation of perikaryon even out into the processes. Dockrill's silver stain; × 400.

The vacuoles were arranged around the periphery of the cell, and the more central, perinuclear portion appeared relatively normal, with well stained and orderly tigroid bodies (fig. 4). No fat was present in these cells.

Similar vacuolated cells, presenting varying degrees of chromatolysis, sometimes accompanied with an increased number of satellites or undergoing actual neuronophagia, were occasionally seen in the basal ganglia also. Figure 5 shows such cells in the thalamus, where their condition more nearly resembled the "severe cell disease" of the German authors. These cells,

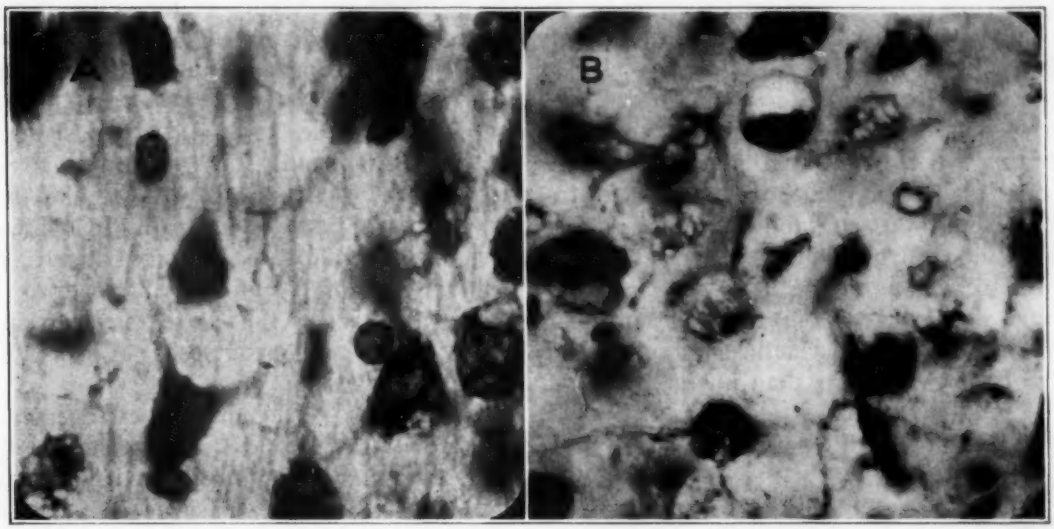

Fig. 3.—*A*, swelling and liquefaction of astrocytes among vacuolated nerve cells in the outer cortical layers. Dockrill silver stain; × 400. *B*, swollen oligodendroglia cells among the vacuolated nerve cells in the outer cortical layers. Dockrill silver stain; × 400.

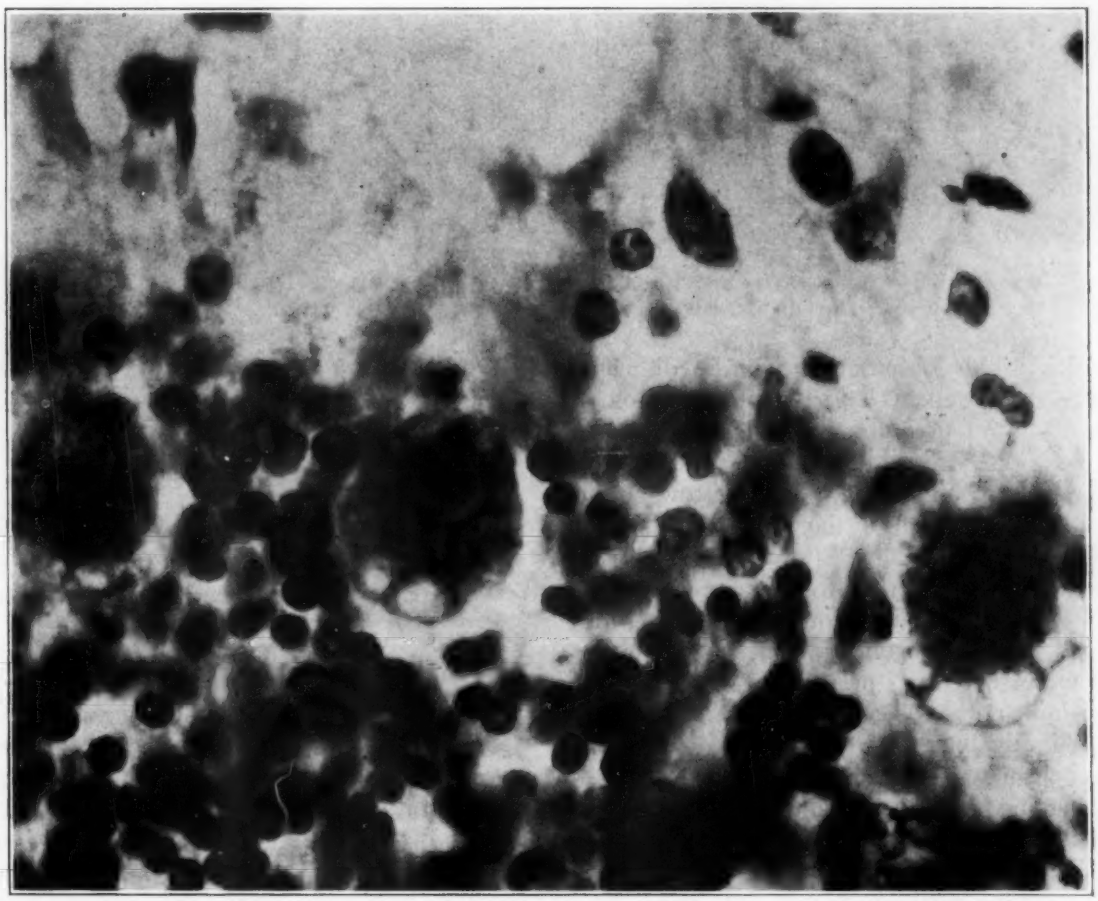

Fig. 4 (dog Horace).—Swelling and vacuolation of the Purkinje cells. Nissl stain; × 400.

however, were not very different from a lesion of type 2 to be described later.

The difficulty in interpreting this type of reaction hinged on the fact that it was largely an exaggeration of the milder, less extensive change that is occasionally observed in the brains of normal dogs which have been prepared in the way these brains were. In the control series were found cells that were vacuolated and chromatolytic to a slight degree; and when they were present in the controls they were located in the same general regions of the brain as in the experimental dogs, that is, in the supragranular layers of the cortex, and chiefly on the external surfaces of the gyri rather than in the depths of

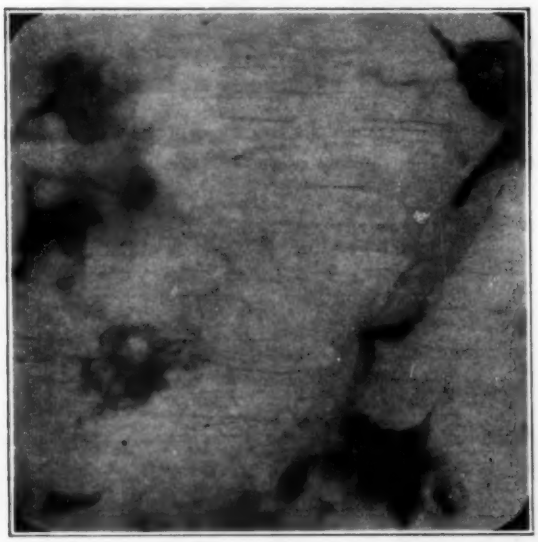

Fig. 5 (dog Flora).—Chromatolysis and vacuolation of cells of the thalamus. Nissl stain; × 400.

the sulci. This observation will be discussed in more detail later. The remaining histologic alterations presented no such diagnostic problem.

From the granular layer inward toward the subcortical white matter the chief ganglion cell disease was "shrinkage." Both ischemic and "chronic" shrinkage types were present, with the latter often more numerous and more conspicuous. These shrunken cells in the deeper layers were sometimes present, as in dog Snowball, when no swollen vacuolated cells were present in the outer cortical layers. The cells of the chronic shrinkage type (fig. 6) were darkly stained; the cell bodies were elongated, with slightly concave surfaces; the processes were hyperchromatic throughout their extent, and the entire perikaryon was pyknotic. The shrunken cell body, together with its apical dendrite, was often twisted into a corkscrew shape or otherwise distorted, and frequently such cells were surrounded by satellites (fig. 7). When ischemic shrinkage types were present, all degrees of paleness were encountered, down to complete invisibility of the cells. Sometimes several such cells would have disappeared in one spot, creating a minute acellular zone (fig. 8), like Spielmeyer's *Herde* or the "pale areas" reported by Gildea and Cobb. Long, sharp, hyperchromatic, spikelike processes were frequently found with these shrunken cells, like those reported in the work of Gildea and Cobb.[6] These shrunken cells were scattered fairly densely among cells of a more normal nature, but in some regions of the cortex in certain cases entire zones were composed of cells of these shrunken types.

With regard to the glia in these deeper cortical layers, it may be said that oligodendroglia cells were increased in number, occurring chiefly as satellites around diseased nerve cells—in contradistinction to the oligodendroglia cells normally found in the areas of "pseudoneuronophagia"[24] of the deepest cortical layers just overlying the white matter. The increased satellitosis spoken of in this paper means the accumulation of glia

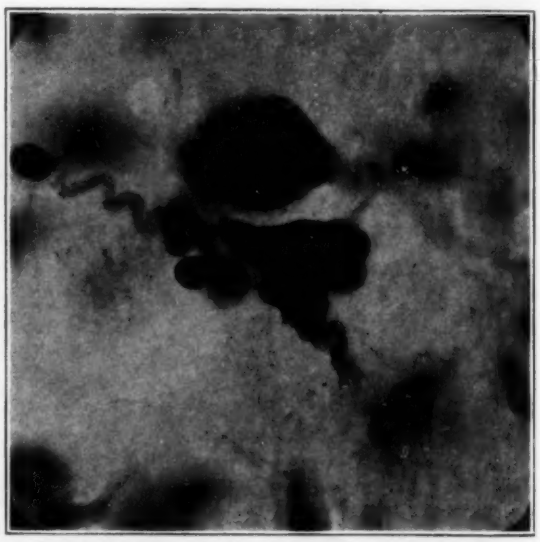

Fig. 6 (dog Horace).—"Chronic shrinkage" in deeper cortical layers, with hyperchromatic, tortuous processes. Nissl stain; × 400.

cells around Betz cells or other definitely diseased cells which normally have no, or few, satellites (fig. 27). Astrocytes also presented certain signs of hyperplasia, often becoming enlarged, containing two nuclei or being in the process of division, with paired daughter cells frequently seen. With Cajal's gold chloride–mercury bichloride stain the processes were often thick and extensive, but Holzer preparations showed no gliosis (fig. 9). The microglia

24. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 493.

cells were inconspicuous. As gitter cells laden with fat, they were present in a meager, scattered sort of way in the perivascular spaces and lying free in the parenchyma. In addition to this, in Nissl preparations hyperchromatosis of microglia cells with polymorphic nuclei was seen fairly often; but unless there was more severe damage than has previously been described, even this low degree of activation of the microglia was scattered, isolated and insignificant.

The blood vessels, except in certain specific conditions, to be described later, presented a moderate amount of thickening, characterized by endothelial and adventitial proliferation. The adventitial overgrowth, seen best in the Perdrau preparations, was confined chiefly to capillaries, but the endothelial hyperplasia was seen better in the smaller arteries and veins. The perivascular spaces were fairly widely dilated and presented a spongy, reticulated appearance. This dilatation extended inward to about the same depth as did the swollen, vacuolated cells.

Summary: This first type of lesion in the gray matter fell short of true necrosis. The ganglion cells in the supragranular layers were usually swollen, vacuolated and chromatolytic, and the glial changes were regressive. In the deeper layers the cells were shrunken, pyknotic and hyperchromatic, with tortuous or spikelike processes, and were often accompanied with increased glial satellites. The microglia cells were not conspicuous.

Lesions of Gray Matter: Type 2.—Fewer than half the dogs presented this second type of lesion, as a glance at table 1 will show. Most of the dogs that were repeatedly exposed to atmospheres with the lower oxygen percentages, and some dogs not exposed to such severe anoxia exhibited this type of reaction. It was found in the cortex or in the basal ganglia, chiefly the thalamus, but was not seen in the medulla, the pons or the cerebellum. These lesions were not all of the same age; so the microscopic picture varied from one animal to another. In the earliest lesions there might be thickening of the vascular walls, with the endothelial nuclei of a longitudinally cut vessel touching one another in the Nissl or the hematoxylin and eosin preparations, while the Perdrau stain would show hyperplasia of vascular reticulum. Van Gieson preparations showed no collagen over-

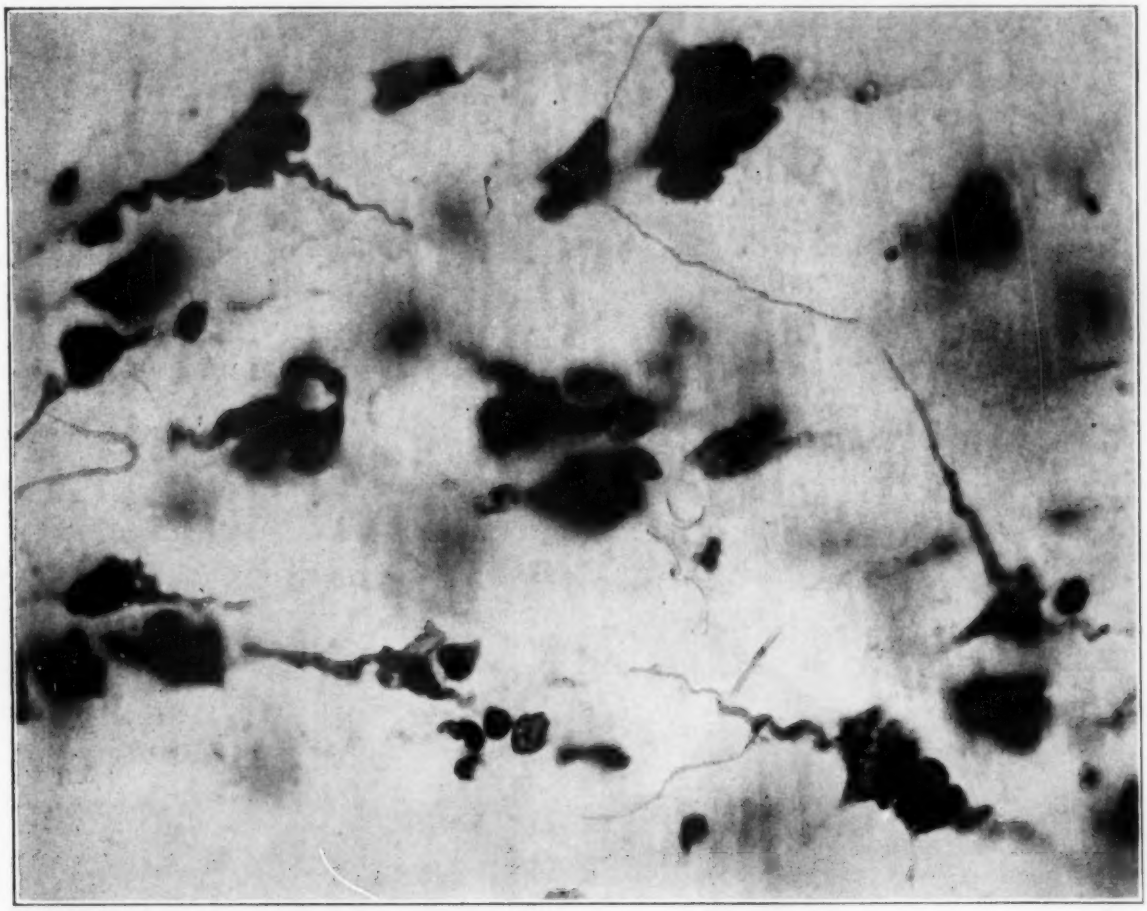

Fig. 7.—Severe "chronic shrinkage" with neuronophagia in the infragranular layers. Nissl stain; × 400.

growth. Sometimes the perivascular spaces were cuffed with hematogenous cells, chiefly lymphocytes (fig. 10), but this was not a frequent feature; and when it did occur it was in the more central portion of such a lesion, the vessels on the edge being merely thickened. In the parenchyma itself in such a focus the ganglion cells might be chromatolytic and pale, although occasionally dark-staining cells were found, and they might be accompanied with an increased number of satellites, which in some cases had begun to invade the region of the disappearing cell body. The oligodendroglial nuclei were pyknotic with the Nissl stain, and in the Dockrill preparations their processes rarely and the perikaryon readily took the Nissl stain and appeared as a pale, bushy fringe, conforming to the shape of the nucleus. These microglia cells not only occupied the space among the ganglion cells but constituted the chief component of the glia participating in satellitosis and neuronophagia. In such a lesion there was often a paling of the myelin, but no fat was present in the earliest stages. The neurofibrils in such a focus were virtually intact.

As these foci of incomplete necrosis advanced in age, all the elements involved underwent further change, either progressive or degenerative. In the Nissl preparations, the blood vessels were observed to continue their hyperplastic trend,

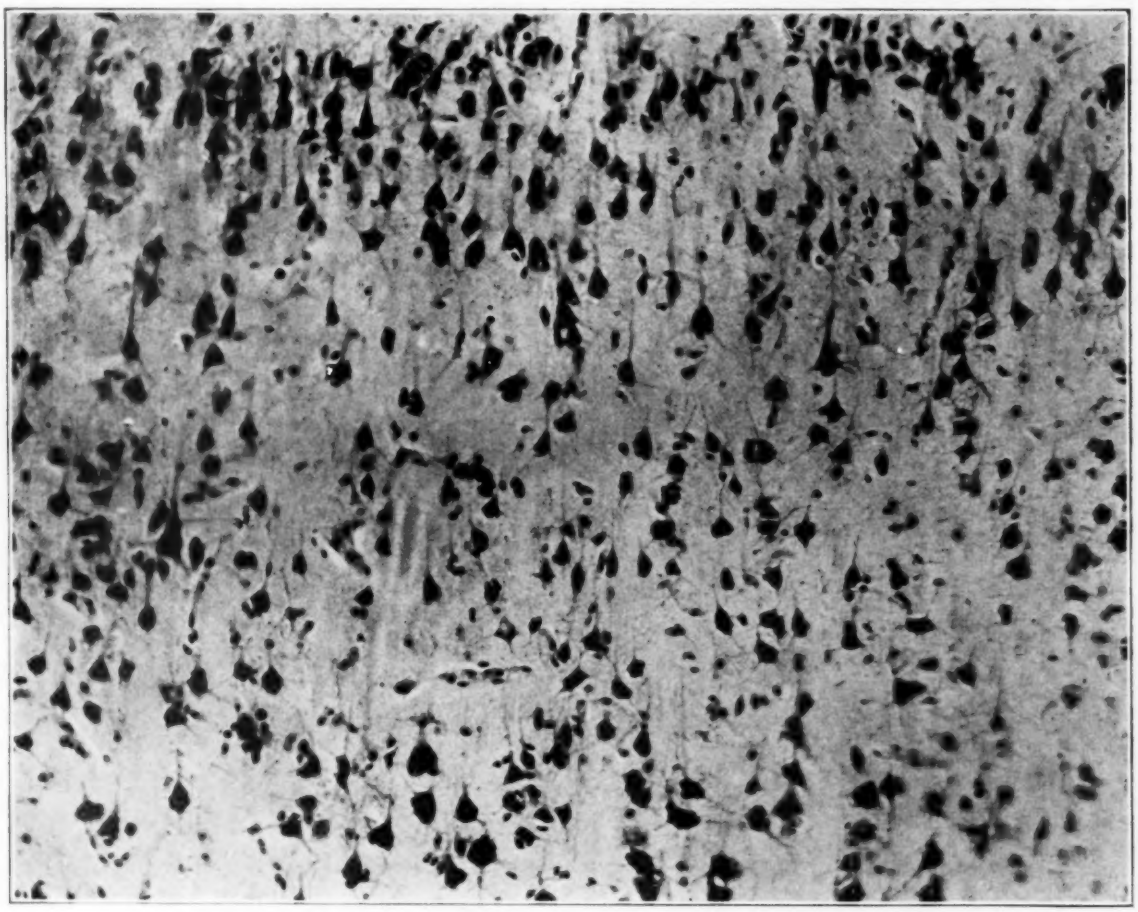

Fig. 8 (dog Casper).—Minute acellular foci in the cortex. Nissl stain; × 100.

took the silver stain, although at the periphery of the lesion swollen oligodendroglia cells were common. In these early foci astrocytes were inconspicuous, and with the Nissl stain their nuclei were often visible but practically always pale and disintegrating, as though undergoing lysis. The cells that attracted immediate attention were the microgliocytes. The entire zone might be closely packed with them. In the early lesion which is being described their nuclei were hyperchromatic, hypertrophied and pleomorphic, with thickening of the walls, budding of endothelial cells and formation of new blood vessels. They lost any cuffing of hematogenous cells they might have had and were often surrounded instead by compound granular corpuscles. Most of the ganglion cells had completely disappeared, but the remaining ones often appeared fairly normal. The oligodendroglia cells in the depths of the focus, and the astrocytes as well, were reduced to occasional pyknotic nuclei or were entirely absent. The microglia cells might

be in any stage of activity, from the polymorphonuclear type to the gitter cell, and sometimes the entire focus would be made up of the latter (fig. 11). The myelin in such a spot was now

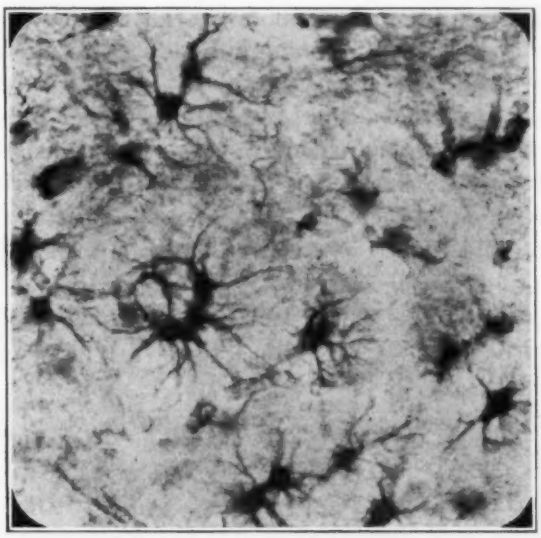

Fig. 9 (dog Terry).—Slight astrocytic hyperplasia in deep cortical layers. Dividing astrocytes were fairly common, but fibrous gliosis was scanty. Cajal's gold chloride–mercury bichloride; × 100.

broken down, and in the oil red O preparation neutral fat was visible everywhere, the granular corpuscles being laden with it, not only in the

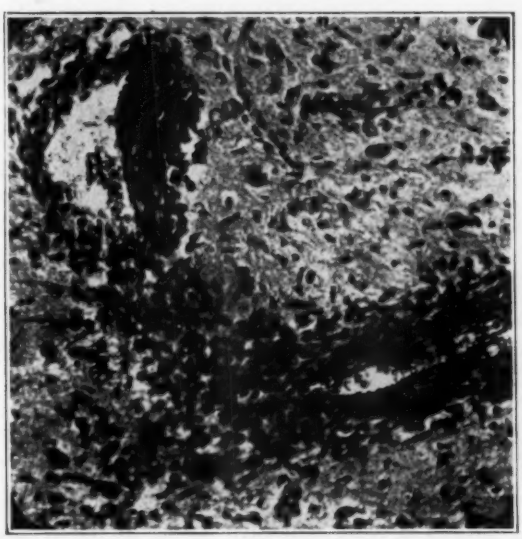

Fig. 10 (dog Hector). — Perivascular cuffing with hematogenous cells, chiefly lymphocytes, in the thalamus. Nissl stain; × 100.

perivascular spaces but throughout the parenchyma. With this stain the vascular endothelium, also, was seen to be well filled with bright red fat droplets (fig. 12). The Spielmeyer or the Weil stain showed loss of myelin, varying from mild to total, while the neurofibrils, although presenting thickenings and tumefactions, were often retained in relatively good condition. The astrocytes in such a focus, when seen in a Cajal preparation, showed occasional feeble attempts at hyperplasia, daughter cells being seen at the periphery of the lesions; but in general the cell bodies, and the processes as well, were granular or fragmented, and in the

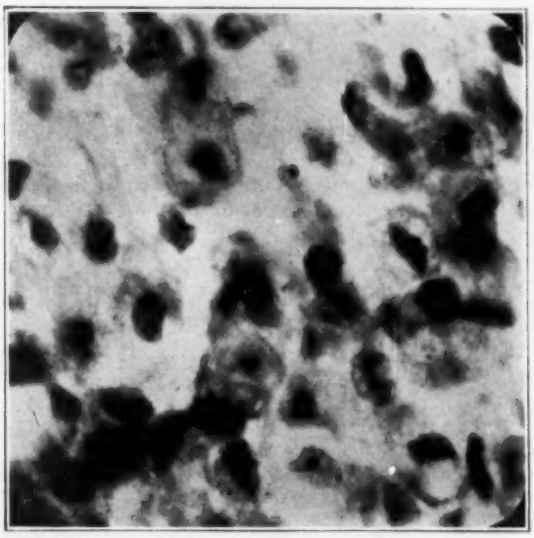

Fig. 11 (dog Flora).—Compound agranular corpuscles in a necrotic focus in the thalamus. Nissl stain; × 400.

depths of the focus the astrocytes were absent. Of course, there was no reaction to the Holzer stain.

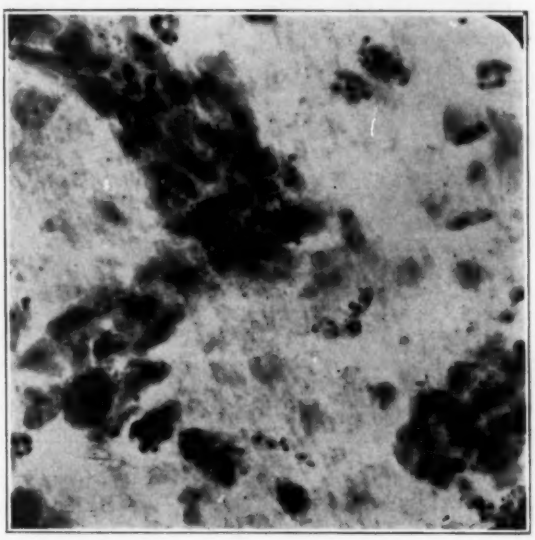

Fig. 12 (dog Hector).—Fat-laden gitter cells, as well as fat, in vascular fibroblasts. Oil red O stain; × 300.

Summary: The second type of lesion of the gray matter consisted in various degrees of necrosis, marked by loss of nerve cells through lysis or neuronophagia, thickening of vascular walls, hyperplasia of microglia cells, fatty ne-

crosis of myelin, perivascular cuffing with hematogenous cells and formation of gitter cells.

Lesions of White Matter: Type 1.—The lesions of the white matter have also been subdivided, for purposes of description, into two groups; but this subdivision is rather arbitrary, and three groups might have been named instead of two, or perhaps all three might have been included under one head and described as different stages of one type of lesion as seen with different stains. This possible relation will be considered in the subsequent discussion. What has been called the type 1 lesion consisted in macroscopic pallor of the white matter as seen with the Weigert, Weil or Spielmeyer stain. The lesions were found almost entirely in the subcortical white matter, and most commonly in the centrum semiovale (fig. 13). The corpus callosum was often involved also, but the central fingers of myelin which extended into the gyri, especially those from the centrum semiovale, were the chief foci of involvement. The temporal lobe was less commonly affected than the frontal, parietal and occipital lobes. The cerebellum was not a usual site of attack, but in 1 case, for example, in which the lesions did strike there they were extensive (fig. 14). These lesions of type 1 were seen to better advantage in the monkeys than in the dogs, but the earlier stages were found most often in the latter. At times the lesions were perivascular, and at other times any connection with blood vessels was not obvious. The blanching of the myelin sheath as shown with Weil's stain was often unaccompanied with any neutral fat in the sections stained with oil red O, and in

Fig. 13 (dog Terry).—Loss of myelin in the subcortical white matter, centrum semiovale and corpus callosum. Modified Weil stain; × 4.

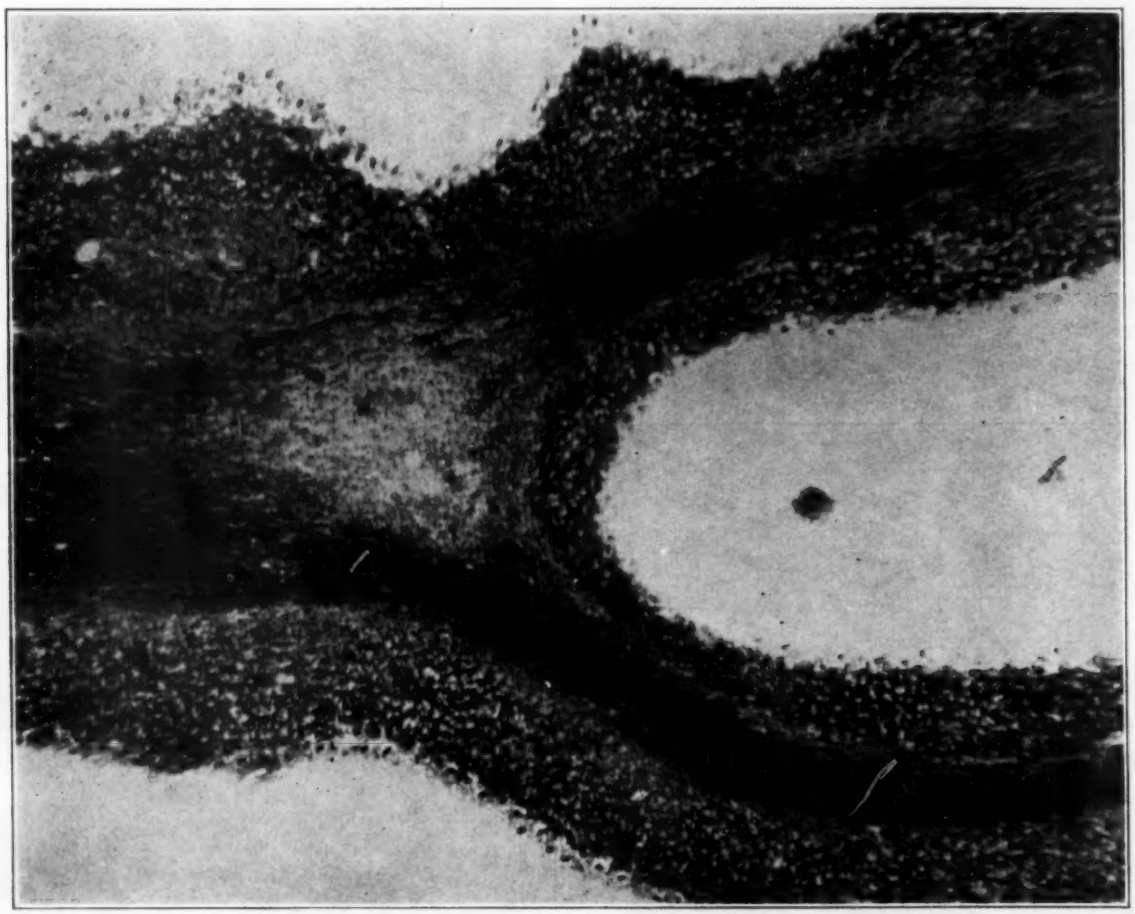

Fig. 14 (dog White Devil).—Small focus of demyelination, part of a more extensive lesion, in the cerebellar white matter. Weigert stain; × 30.

polarized light there was still double refraction in most places. Examination with a high power lens revealed swollen sheaths in the depths of the lesion, accompanied with myelin figures, but toward the edge of the lesion the sheaths appeared merely pale, without any irregularities. This indicates that the lesion was usually slightly older at the center than at the edge; indeed, when the lesion was more advanced in age than that which has just been described, fat was present in the central portion before it appeared at the edge. This observation will be mentioned again.

poral lobe and in the cerebellum. They were not seen in the medulla or the spinal cord.

The usual appearance with the Nissl stain (fig. 15) was a reaction of interstitial cells in the subcortical white matter. A cluster of blood vessels with thickened walls might be surrounded by a field of hyperplastic microglia cells with pleomorphic nuclei, forming fairly dense collars about the individual vessels and gradually diminishing in numbers and in degree of activation until normal fields were reached at the periphery of the focus. The picture was not always the same because the age of the lesions varied from

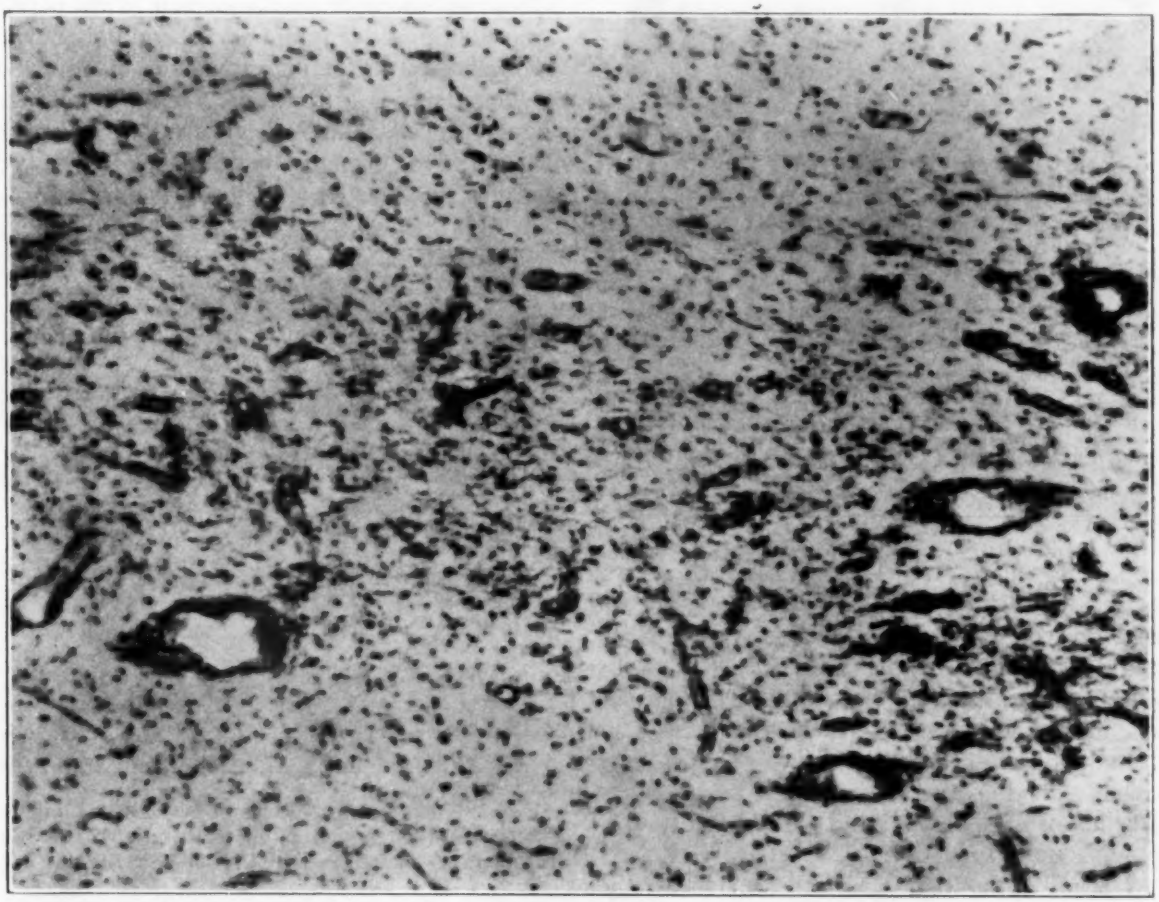

Fig. 15 (dog Peter).—Typical focus in the centrum semiovale, with thickened blood vessel walls in the midst of pronounced microglial hyperplasia. The overcellularity throughout the field consists in hyperplasia of microglia cells with pleomorphic nuclei. Nissl stain; × 100.

Lesions of White Matter: Type 2.—The cellular reaction is the chief feature of this type of lesion, and, as previously mentioned, it is intimately associated with the demyelination of the first type of lesion of the white matter, which is characterized by pallor. The site of the lesions was the same as that of the type 1 lesions, namely, in the subcortical white matter of the various convolutions, and especially in the centrum semiovale. Such lesions occurred in all lobes of the brain, but less frequently in the temone animal to another, although the age was probably always about the same in different regions of the brain in any one animal. There might be hematogenous cells in the perivascular cuffing, consisting chiefly of lymphocytes but occasionally of a few polymorphonuclear leukocytes. At a later stage compound granular corpuscles might be found in the Virchow-Robin space or in the parenchyma beyond. The hematogenous cells were never seen in the parenchymatous tissue. Among the hyperplastic microg-

lia cells, plump astrocytes, *"gemastete* cells," were sometimes present (fig. 16). The walls of the blood vessels varied in thickness from normal capillaries with a single row of endothelial cells to those with endothelium four or five rows thick. Longitudinally cut vessels might show endothelial nuclei touching one another, and even piling up in greater numbers. Often the vessel looked thicker in sections stained with the Nissl method than the number of endothelial nuclei would warrant; in such cases the Perdrau stain showed a dense overgrowth of reticulin, while the Van Gieson stain did not show much increase in collagen. In the Nissl or Dockrill preparations long rows of oligodendroglia cells (fig. 17) were often found along these capillaries, and other small vessels, when they were cut longitudinally, and when similar vessels were stained with Perdrau's method, hyperplasia of the reticulin was encountered. This will be discussed later.

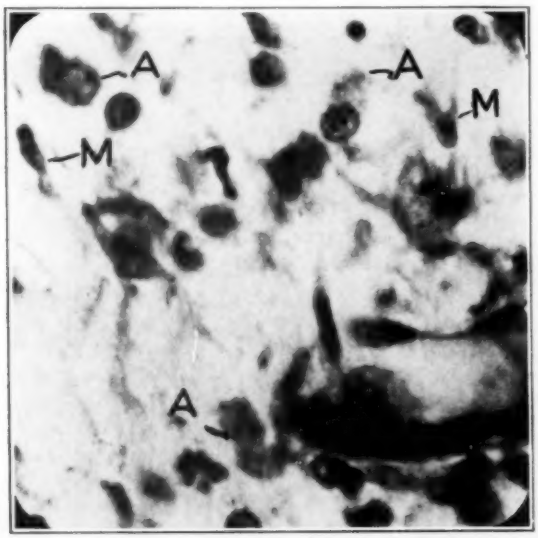

Fig. 16 (dog Peter).—Plump astrocytes (*A*) among the microglia cells (*M*). Nissl stain; × 300.

As regards the relation of these cells to the structures they lie among, it was seen with the stain for fat that the great majority of these polymorphonuclear microglia cells contained no fat in their cytoplasm. Of all the forms of glia cells, only the full-fledged gitter cells, lying chiefly in the perivascular spaces, or close to them, contained fat. In addition, the endothelial cells of the blood vessels were often stippled with granules of neutral fat. Even though the Weil stain showed paling of the myelin in the neighborhood of such a zone, as has previously been mentioned, the amount of the fat in these early lesions was extremely meager. Furthermore, it was often noticed that the gitter cells scattered free in the tissue were of conspicuous size but only a pale straw color, rather than bright red, with the oil red O stain. With crossed Polaroid these gitter cells were seen to contain material that was still anisotropic. The nuclei were indistinguishable from the microglial nuclei of ordinary compound granular corpuscles.[25] Some of the axons passing through this hypercellular zone became thickened, but no severe destruction of axons was present in these early lesions, and practically no signs of axonal reaction could be detected in the neighboring cortical cells.

The sequence of development of these lesions was as follows: alteration of the myelin, hyperplasia of microglia accompanied with perivascular collections of lymphocytes and polymorphonuclear cells, thickening of walls of blood vessels, development of gitter cells, recession of hematogenous cells, fatty degeneration of myelin, degenerative changes in oligodendroglia cells and in some astrocytes, hypertrophy of other astrocytes and swelling of neurofibrils. This sequence will be discussed later, and possible explanations for apparent differences in the order of events will be presented.

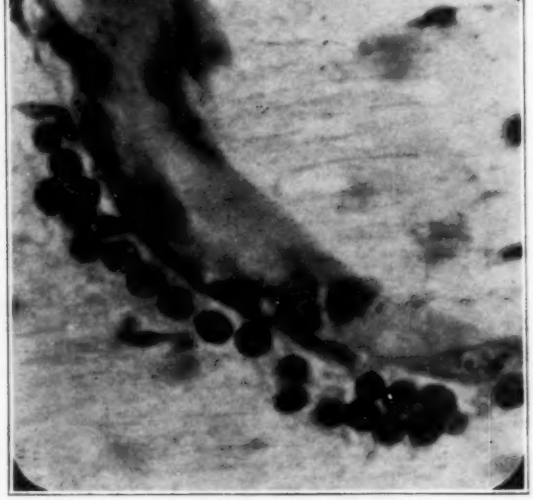

Fig. 17 (dog Peter).—Rows of perivascular oligodendroglia cells, often present in white matter and sometimes in gray matter as well. Nissl stain; × 400.

MONKEYS [26]

GROSS INSPECTION

The 10 monkeys in this study ranged in age from 2 to 4 years and weighed on an average

25. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, New York, Paul B. Hoeber, Inc., 1940, p. 554.

26. Nine of the monkeys whose brains and spinal cords were studied here were observed during experi-

about 4,500 Gm. The weight of the brain was about 90 Gm. Table 2 gives details concerning the altitude reached and the number of exposures experienced by each animal, as well as the mode of death. Few of the animals presented any abnormal signs, but the clinical data on 2 of them deserve mention. Animal P67 showed marked weakness of the hindlegs after each daily exposure. There was apparently complete recovery in about an hour, and no residual signs could be elicited. The brain presented no abnormal features on inspection with the naked eye. Animal P82 on one occasion two months before death had a right-sided epileptiform convulsion. The brain appeared normal except for a pale yellow, shallow depression in the occipital lobe, running in a coronal plane midway between the sulcus lunatus and the tip of the lobe, and a second, smaller, depression on the superior margin of the postcentral gyrus. These regions felt soft to the touch. The other animals showed no abnormal conduct during the experiments. The brain of monkey P80 presented a yellow, depressed streak on the left postcentral gyrus, extending out into the superior parietal gyrus. The brain of monkey P66 presented unusual engorgement of the pial vessels. On section, several of the brains exhibited grayish, slightly roughened patches in the region of the centrum semiovale; otherwise, nothing remarkable was noted.

TABLE 2.—*Data on Ten Monkeys Exposed to Daily Anoxia in Decompresison Chamber*

Monkey No.	Number of Experiments	Number of Days	Oxygen, %*	Lesion: Gray Matter Type 1	Gray Matter Type 2	White Matter Type 1	White Matter Type 2
P61	5	5	7	..	..	..	..
P64	5	5	7	±	..	+	..
P65	15	15	6	+	..	..	..
P66	40	40	6	+	..	+	+
P67†	47	47	6	+	+	+++	+
P78	96	96	6	+	..	+++	++
P80†	112	112	6	+	+	+	+
P81†	112	112	6	+	..	+++	+
P82†	114	114	6	+	+	++	+++
1633	1	1	6	..	+++	..	..

* Animal breathed room air at a pressure of 275 or 225 mm. of mercury.
† Animal was killed with pentobarbital sodium.

ments under lowered barometric pressure in a decompression chamber in the laboratory of the Aviation Medicine Unit, Division of Industrial Hygiene, National Institute of Health, United States Public Health Service, Bethesda, Md. The material was furnished through Surgeon Benjamin F. Jones, United States Public Health Service, and Dr. Frederic D. Chapman, formerly Assistant Surgeon (R), United States Public Health Service. Their physiologic observations have not yet been published, although some have been reported to the Committee on Aviation Medicine of the National Research Council. The other monkey brain (1633) came from the department of physiology at Yale University, through Dr. John Fuiton.

MICROSCOPIC EXAMINATION

The same division of lesions into types occurring in the gray matter and types occurring in the white matter obtained with the monkeys as with the dogs. In the monkeys, however, the changes in the gray matter were less pronounced, while the alterations in the white matter were more pronounced, than in the dogs.

Lesions of Gray Matter: Type 1.—The combination of alterations in the nerve cells characteristic of this type was found to some extent in every case. In the supragranular layers the vacuolation was of a slightly different character from that seen in the dogs in that the vacuoles were usually smaller and more closely crowded about the edge of the cell. The chromatin, instead of being vitreous in appearance, might be darkly stained, and the nucleus was usually pyknotic. There was but little glial accompaniment. These vacuolated cells were not universally distributed in the supragranular layers but occurred in clusters or in zones. Sometimes in one section most of the cells of the outer layers of an entire gyrus might be affected, while neighboring convolutions showed relatively few vacuolated cells. Then, too, in the deeper layers this vacuolated type of change was sometimes encountered in single cells or in small groups of cells, but here the reaction was apt to be of a more advanced nature. Betz cells, for example, might have the vacuolation of cytoplasm, the streakiness of chromatin and the satellitosis characteristic of severe cell disease. These scattered, vacuolated cells of the deeper layers were found among the shrunken cells so commonly seen in these brains. Extremely concave bodies, sometimes pale and sometimes deeply stained, with corkscrew processes in some instances and spike-like processes in others, and with the nucleus often eccentrically placed and pyknotic, characterized these shrunken cells. Sometimes they were accompanied with oligodendroglial or microglial nuclei. Pale areas caused by lysis of small groups of cells did not seem as common in the monkeys as in the dogs, although there were in all cases scattered ghost cells so pale as to be scarcely visible. In the cerebellum, in the majority of cases, long rows of Purkinje cells frequently showed large vacuoles around the periphery, with the rest of the cell in fairly good condition, though perhaps slightly hyperchromatic. Sometimes, however, rows of skrunken, pyknotic, hyperchromatic cells with overstained processes were visible. The granular cells were not noticeably affected.

Lesions of Gray Matter: Type 2.—This type of lesion was virtually nonexistent in most of the monkeys of the P series. The only animals of this group to show this severe type of reaction in the cortex were monkeys P80 and P82. The former had a severe lesion in the left postcentral gyrus and the latter a lesion in the left occipital lobe. In addition, monkey P67 presented a small lesion in the thalamus. While these lesions were distinctly different from the lesion of type 1, just described, they were not quite identical with the lesions of type 2 in the gray matter of the dogs. In the dogs the pathologic process was more nearly that of incomplete necrosis, while in the monkeys typical foci of softening were encountered in the gray matter. But all these changes were, to some extent, relative. The ganglion cells were destroyed along with the myelin sheaths, axons, oligodendroglia cells, astrocytes and even blood vessels. The intensity of changes in the lesion diminished toward the periphery, the focus being closely packed with fat-laden gitter cells in the deeper portions and only moderately so farther out. In the relatively sound tissue beyond the zone of granular corpuscles, ameboid astrocytes were in profusion, giving a clue to the age of the lesion. Practically no fibroblastic proliferation was encountered. These lesions were entirely cortical in extent and included virtually the entire depth of the gray matter at their greatest penetration, shading off gradually, so that at the periphery only the outer molecular layer was involved. No such lesions were found in the basal ganglia.

Incomplete necrosis of the gray matter was found in another animal. Macacus monkey 1633 is described separately because the microscopic picture was unique in the series, although practically identical with that of lesions in human brains described by other investigators,[27] an observation which will be discussed later. This animal was subjected to standard progressive decompression, the pressure reaching that at a simulated altitude of about 32,500 feet (10,600 meters), or 200 mm. of mercury, in twenty-three minutes. On recompression, several minutes of artificial respiration was necessary. When let loose in the runway, the animal appeared slug-

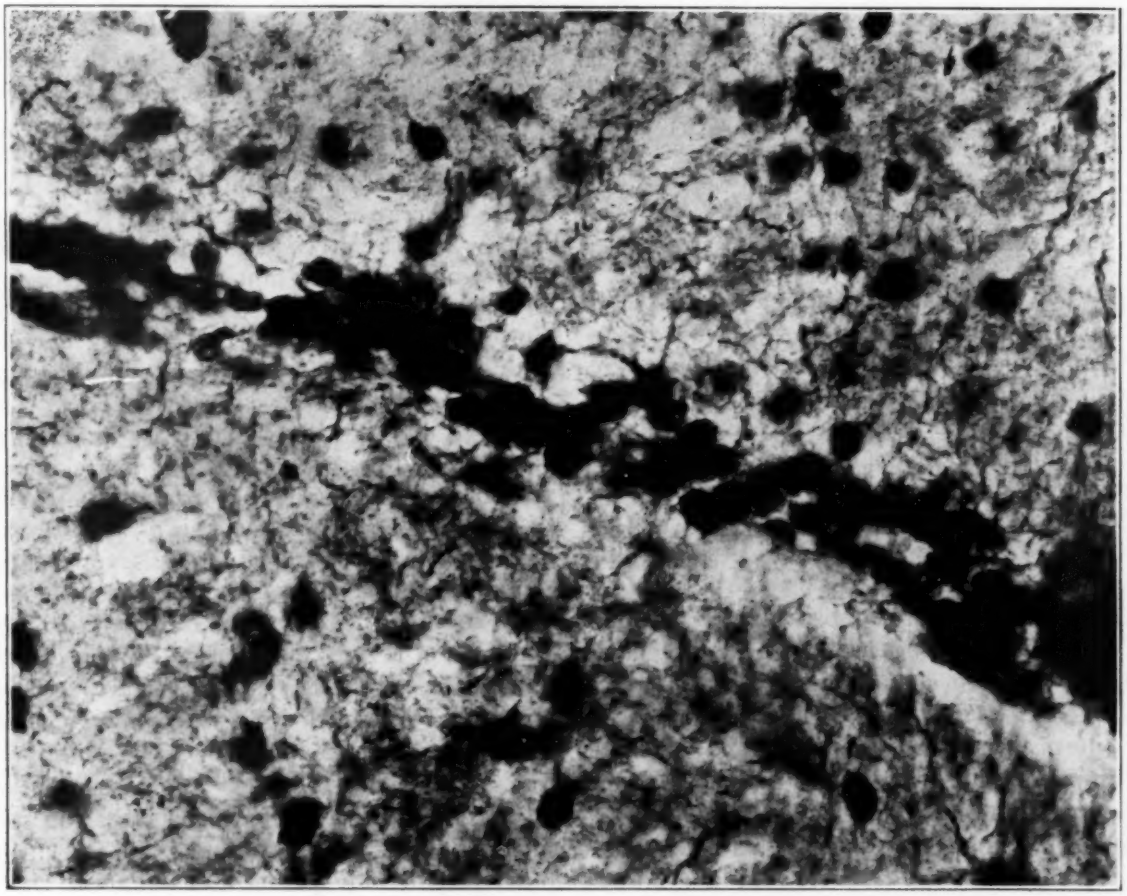

Fig. 18 (dog Flora).—Long rows of perivascular oligodendroglia cells. Dockrill stain; × 400.

27. Stewart, J. D.: Cerebral Asphyxia During Nitrous-Oxide and Oxygen Anesthesia, New England J. Med. **218**:754, 1938. Courville.[5]

gish, ataxic and weak on the right side and showed slight forced grasping in both forelimbs and hindlimbs. The animal improved during observation, but eight days later it was seen to climb slowly, use its fingers poorly and drag the fingers of the right hand when walking. The next day, nine days after the decompression, the animal was killed with ether.

Postmortem examination showed the brain to be under increased intracranial pressure. The microscopic lesions were extensive. They were confined almost exclusively to the gray matter, being most often present in the third, fourth and fifth cortical layers in the frontal, parietal and occipital lobes. The temporal lobes were singularly free from disease, as were the pons, cerebellum and medulla. There was a well circumscribed focus in the globus pallidus.

The Nissl stain showed dense thickening of the blood vessel walls, with increased cellularity of the endothelium, adventitial hypertrophy and formation of new capillaries. The nerve cells were severely affected, over half of them being destroyed in any region which was involved. Swelling, chromatolysis and vacuolation of the cell body, with eccentricity and swelling of the nucleus, extensive satellitosis and neuronophagia, were commonly observed. Compound granular corpuscles were abundant throughout the affected fields, while astrocytes and oligodendroglia cells showed regressive changes. Clusters of microglia cells with rod-shaped nuclei were seen in the less severely affected zones, and nodules of oligodendroglia cells were frequently found in the sites of former nerve cells. In the myelin preparations the most striking lesions were seen. Extensive, patchy demyelination, in the form of "moth-eaten" spots, throughout the three affected layers was the usual change observed. Figure 19 shows such a patch, with interruption of the fan fibers passing through the diseased zone. The oil red O stain showed that this region was filled with fat, broken-down myelin sheaths, fat-laden gitter cells and astrocytes and nerve cells undergoing fatty degeneration. Fatty degeneration of the nerve cells was not so extensive as might have been expected from the severity of the lesion as seen with the Nissl and myelin stains. Bodian silver preparations showed many intact, normal axons traversing the affected zones, although most of them had become granular and fragmented. Swelling and thickening

Fig. 19 (monkey 1633).—Extensive laminar seminecrosis, with loss of fan fibers in the cortex. Spielmeyer stain; × 30.

of axons were not common. Hortega's stain for microglia showed all stages of development of gitter cells, as well as small clusters of rod cells ("glial bushes"). There was no Holzer reaction, and the amount of collagenous hyperplasia was limited; but Perdrau's stain (fig. 20) showed dense hyperplasia of reticulin in the adventitia of vessels in the zones of the lesion. The thickened walls of blood vessels and the formation of new vessels in the midst of a zone of seminecrosis presented the appearance of what Courville [5] described as an "astrovascular scar," al-

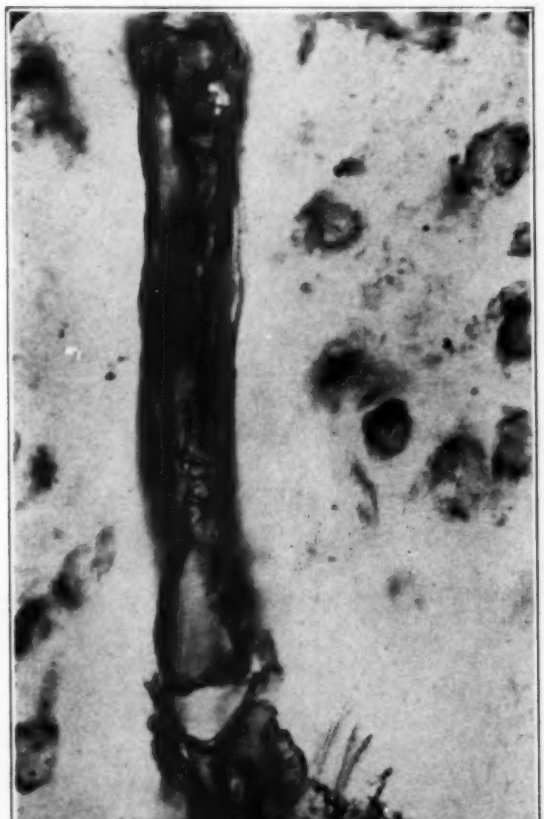

Fig. 20 (monkey 1633).—Hyperplasia of the reticulin. Perdrau stain; × 400.

though proliferating astrocytes were certainly not present in this case and it is difficult to tell from Courville's illustrations that they were present in his cases.

Lesion of White Matter: Type 1.—The most obvious lesion of the entire series was the macroscopic blanching of the tongues of subcortical white matter as they extended into the various gyri, as seen with the Weil stain (fig. 21). As table 2 shows, the first 3 monkeys, none of which had more than 15 exposures, did not present this lesion, but all the animals that received 40 or more exposures were affected. The disease extended from the frontal to the occipital pole, with perhaps slightly less involvement of the temporal than of other regions of the brain. The cerebellum was occasionally involved. Secondary degeneration of the pyramidal tracts could be followed into the spinal cord. As in the dogs, the centrum semiovale was the site of predilection, with involvement of the neighboring subcortical marrow, as well as the corpus callosum. The lesion tended to conform in shape to the shape of the mass of white matter in which it was situated, being long and narrow where the white matter was long and narrow, broad and fan shaped where the white matter was broad and fan shaped and triangular where the white matter was triangular. The lesions were invariably located in the more central regions of the white matter, leaving at all times a rim of relatively intact myelin between the diseased tissue and the normal gray matter. It is pointed out that this distribution is reminiscent of Schilder's disease (progressive subcortical encephalopathy), and this point will be discussed later in connection with other types of anoxia.[28]

Microscopically, the appearance varied somewhat with the age of the lesion, and, while this differed in different animals, it is emphasized that in any one animal the lesions were nearly always of the same age whether in the frontal, the parietal or the occipital zone. In the early lesions, especially those which were invisible to the naked eye with the Weil or the Spielmeyer stain, swelling and paling of individual myelin sheaths, some of them with vacuolations and ballooning, were probably the first signs. It is not possible to be categoric on this point because of the character of the cellular reaction, which will be described under lesions of type 2. At first the number of pale sheaths was so slight that they could easily be overlooked. Later, as the disease of the myelin increased in severity, patches of obvious demyelination developed. These consisted of pale, thickened sheaths, swollen irregularly into great vacuolated tumefactions and interlacing with one another so that a fenestrated appearance was given to the affected zone. Fragmentation of some sheaths resulted in glistening *Markballen* lying among the diseased sheaths. With the oil red O stain no fat would be found at this stage of degeneration. With polarized light the Marchi balls were doubly refractile, as were the myelin sheaths themselves (fig. 26). As the age of the lesion increased, the demyelination progressed and was usually

28. Ferraro.[13] Hurst.[14]

most intense in the central zone, fading out gradually to normal tissue at the periphery. Sometimes a blood vessel was located near the most intensely demyelinated part of the focus (fig. 24), but often equally intensely demyelinated foci bore no apparent relationship to blood vessels. Only extremely gradually did the myelin and other structures break down into neutral fat, and in the older lesions this fat was seen with the oil red O stain as bright red globules lying free in the tissue spaces in sparse distribution or engulfed in granular corpuscles, which were by no means numerous except in the oldest lesions, or contained within the endothelium of blood vessels. In a well developed lesion the gitter cells might be massed together, and in the neighborhood of the axons that must have passed through the affected zones in the centrum semiovale often showed marked swelling of the perikaryon, eccentricity of the nucleus and sometimes peripheral pyknosis. But the conventional central chromatolysis of typical retrograde degeneration was rarely present. Often, however, these affected Betz cells were accompanied with satellites, few or many, and occasionally they underwent neuronophagia (figs. 27 and 28).

Lesions of this type were present in the cerebellum in only 2 monkeys, 1 of which showed but few and small foci, while the other exhibited extensive partial demyelination of the subcortical white matter throughout the cerebellar hemispheres.

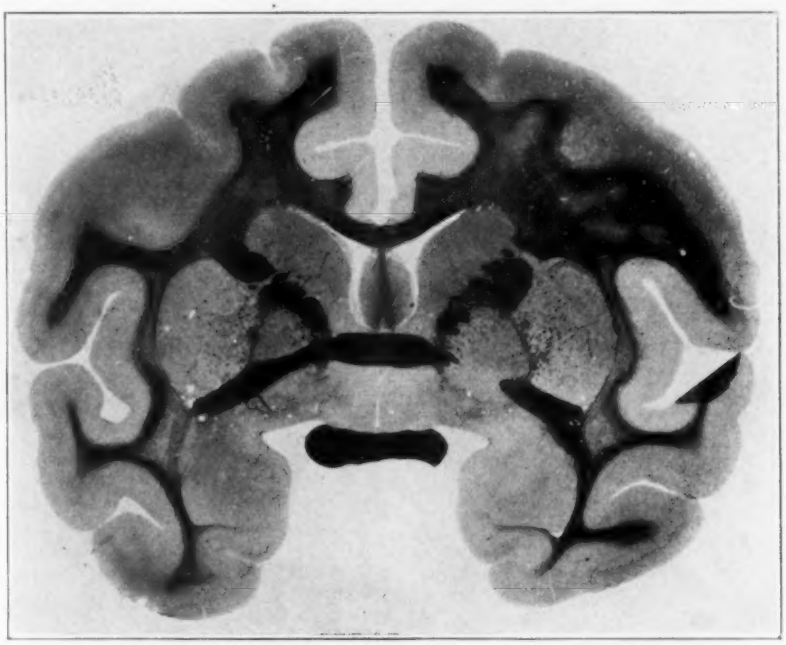

Fig. 21 (monkey P67).—Demyelination and patchy loss of myelin in the centrum semiovale, corpus callosum and subcortical white matter. Weil stain; × 4.

sections stained with oil red O, such as those of monkey P66 (fig. 31), in which a focus of fat-filled microglia cells occurred in the midst of an otherwise mild but extensive lesion, they appeared brilliant red. Further discussion of the microglia is better left to the description of lesions of the white matter of type 2. The loss of myelin was accompanied with alterations in the axons. Thickening of the latter, followed later by moniliform swellings, vacuolation, tortuosity and fragmentation, ending finally in complete destruction, was the usual course of events.

With regard to the effect on the cortical nerve cells of this loss of myelin and destruction of axons, it may be said that advanced axonal reaction was but rarely observed. However, examination of the Betz cells, for example, in

Secondary degeneration resulting from lesions in the centrum semiovale, corona radiata and like structures was traced into the spinal cord of the majority of the animals. Pallor of the corticospinal tracts was visible on inspection with the naked eye of sections stained with the Weil method. With the microscope, swollen sheaths and myelin figures could be seen in the pyramidal pathways.

Lesion of White Matter: Type 2.—In some cases this second type of reaction apparently preceded the demyelination. In monkey P61 there was a slight focus in the centrum semiovale of the parietal lobe in relation to a small blood vessel. In other circumstances, the lesion might have been passed over as one of the many minor variations of otherwise normal structure;

but, being a collection of hyperplastic microglia cells similar to, but smaller than, those to be described, it assumed significance. Animal P65 had a few such small foci, together with hyperplastic astrocytes, in the centrum semiovale and the corpus callosum. It must be pointed out that in neither of these animals was the focus entirely typical of the lesions observed in the 6 animals next in the series, which had received greater numbers of exposures, although it somewhat resembled them.

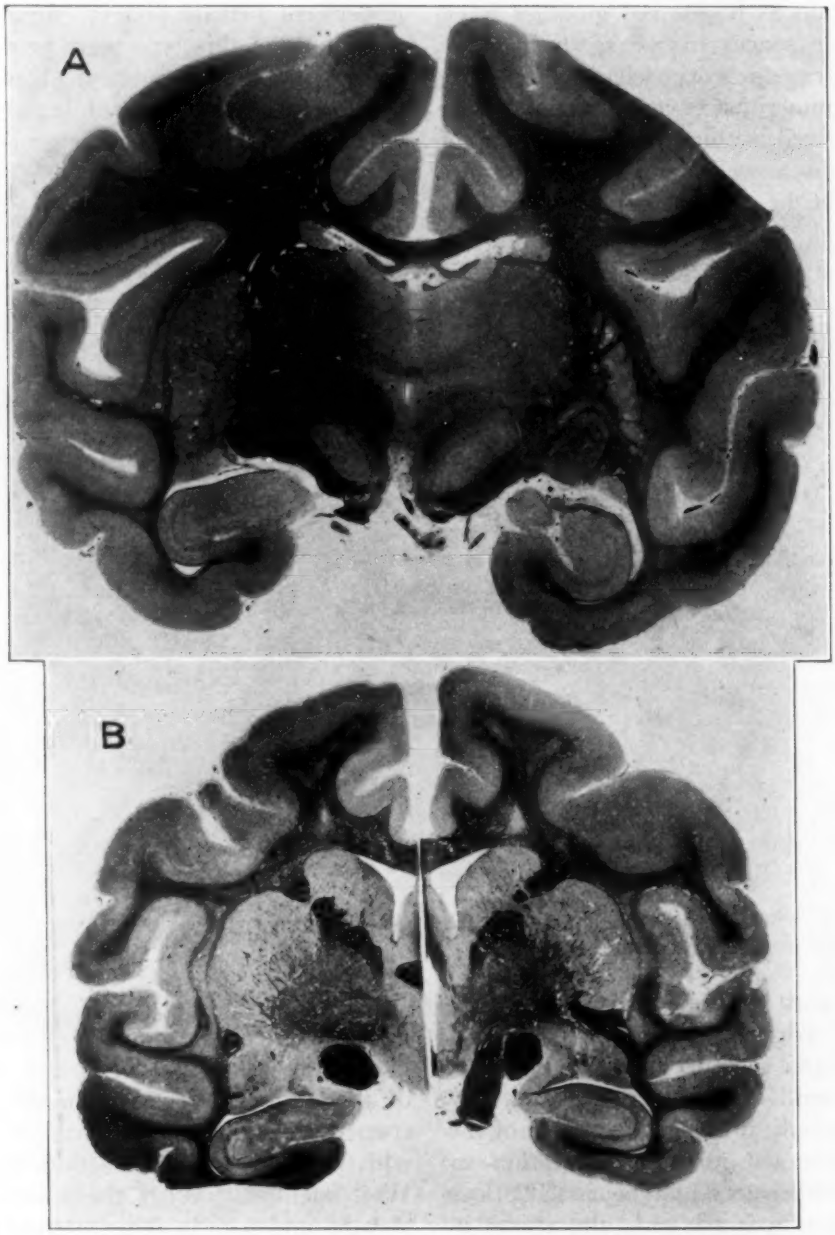

Fig. 22—*A* (monkey P66), early loss of myelin and blanching of white matter in the centrum semiovale and in the temporal lobe. *B* (monkey P82), more extensive loss of myelin. Weil stain; × 4.

As in the dogs, the outstanding feature of these typical, and pathologic, foci was overcellularity; microglia cells, with polymorphic nuclei and bushy perikaryons, sometimes in relation to blood vessels and sometimes not, were found in the subcortical white matter. In some of the lesions these collections of microglia cells were loose and scattered, as in the dogs, while in others they formed tight collars about blood vessels (fig. 29). Most of these cells contained no fat. The blood vessels themselves had thickened walls, all layers being involved in hyperplasia, although formation of new blood vessels was not observed. The cells farther out from the perivascular cuffs were but loosely scattered and consisted not only of bizarre-shaped microgliocytes but of many plump astrocytes, with

their eccentric nuclei, their eosinophilic, homogeneous, waxlike cytoplasm and, in the Nissl preparations, their stubby processes (fig. 30). In certain animals, as in the most severely affected monkey, P67, and in monkeys P66, P78, P81 and P82, foci of active microglia cells containing bright red fat were observed in the oil red O preparations. These gitter cells were usually in the most central part of the demyelinated patch and occupied, depending on the age of the lesion, one tenth or less of the demyelinated zone. As in some of the dogs, hematogenous cells were present in the brain of 1 of the monkeys (fig. 31). The oligodendroglia cells early became swollen, and their processes were unstainable, the nucleus and cytoplasm becoming extremely granular. In the Cajal gold chloride–mercury bichloride stain, the astrocytes in the center of the focus were devoid of processes, and their cell bodies were stippled with coarse granulations (fig. 32). As inspection proceeded from the center of the focus, it was seen that the astrocytes gradually retained their processes, which even farther out resumed their vascular attachments and lost their stippled appearance. Definite signs of hyperplasia were encountered: dividing nuclei, dividing astrocytes and paired daughter cells (fig. 33). With the Holzer stain definite signs of early gliosis were observed. This Holzer reaction was found in all brains which had foci of fatty necrosis, but it was always extremely mild.

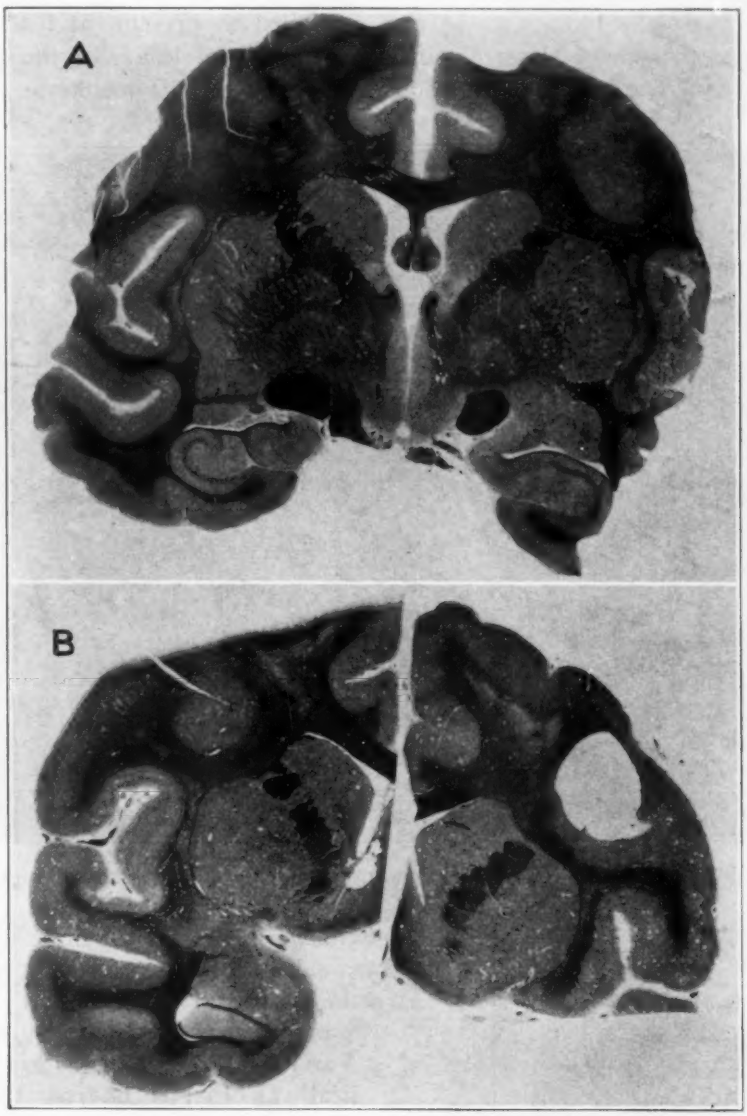

Fig. 23.—*A*, monkey P81 and *B*, monkey P78. Progressively extensive demyelination. Block of brain of monkey P78 was split for other stains; hence the section is not quite symmetric. Weil stain; × 4.

In summary, then, it may be said of these lesions of the white matter that they consisted in demyelination which was of different ages in the different animals. In some animals it had

reached the stage of breakdown of myelin in which neutral fat could be found, and in others no fat had yet been formed. Furthermore, in any one focus of loss of myelin there might be fat and gitter cells in one segment of the lesion and no fat but microglial hyperplasia in another portion, while in the remaining part blanched white matter might appear in Weil or Weigert preparations but the individual sheaths might still show double refraction in frozen sections. It was usually observed, however, that in any one animal, the same pattern of aging obtained in all the foci observed. The lesion in its various parts was approximately of the same age in the frontal, parietal and occipital lobes. This feature was observed formerly by Hurst in cases of cyanide poisoning.[14]

DISTRIBUTION OF LESIONS

The alterations of the nerve cells in the supragranular layers were the most common changes encountered, and they were virtually always present in the frontal lobes. Of the 25 dogs, only 2 failed to present, at least in some gyri, this first type of lesion of the gray matter. Likewise, of the 10 monkeys, only 2 escaped this change in the nerve cells, and 1 of them (1633) could not be expected to show it because of the nature of the exposure. The parietal lobe was also fairly constantly involved; while tables 3 and 4 indicate that this lobe was affected practically as often as the frontal lobe, the impression one has from studying the microscopic slides is that the lesions of the parietal lobe were distinctly less conspicuous. The occipital and temporal lobes were less commonly affected. The latter, especially, was spared more often than other regions of the cerebrum, in spite of reports in the literature concerning the vulnerability of this part of the brain to anoxia because of the peculiarities of its vascular architecture.[29]

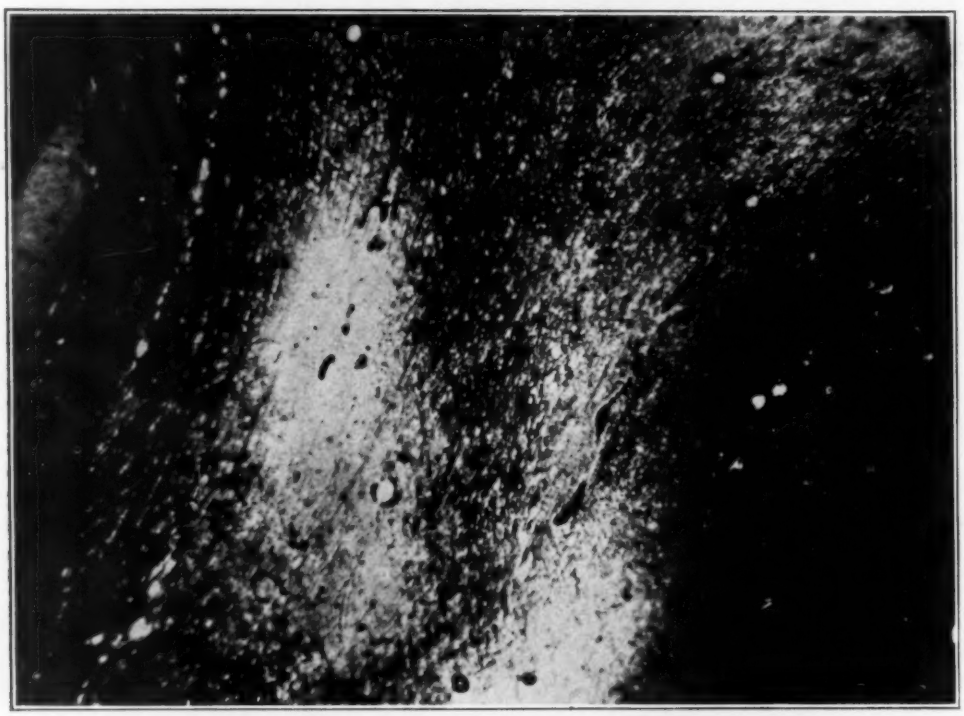

Fig. 24 (monkey P81).—Patches of demyelination in relation to blood vessels. Weigert stain; × 100.

Fig. 25 (monkey P67).—Early loss of myelin in the subcortical white matter. Frozen section; Spielmeyer stain; × 4.

29. Spielmeyer, W.: The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869 (May) 1930.

The cerebellum presented fewer and milder changes, this region being involved in only 10 of the dogs and 5 of the monkeys. As has previously been described, long rows of Purkinje cells were often missing, pyknotic or vacuolated. The granular cells were not involved. There seemed to be no rational system in the selection of cases with involvement of the Purkinje cells, for some of the animals exposed to low degrees of anoxia presented changes, while some of the animals exposed to considerably more severe conditions were normal. The changes in the basal ganglia were more infrequent than those of the cerebellum (simple vacuolation and chromatolysis were not sufficient criteria of disease in cells of this region because of the nature of these cells in normal conditions).

TABLE 3.—*Distribution of Lesions in 25 Dogs Subjected to Anoxia* *

Dog	Frontal Lobe	Parietal Lobe	Occipital Lobe	Temporal Lobe	Basal Ganglia	Cerebellum
Judith	+	+	+	+	..	..
Duncan	..	+	..	..	..	..
Pansy	+	+	+	+	..	+
Lillian	+	+	+	+	..	..
White Devil	+	+	+	+	..	++
						+
Casper	+	..	+	..	++	+
			+			
Allegra	..	+	+	..	..	..
	+					
Oscar	..	..	..	..	..	..
Horace	+	+	+	+	+	+
Sadie	+	..	+	..	..	+
Timothy	+	+	+	+	..	+
			+			
Edwin	+	+	..	..	..	..
	+					
Patricia	+	+	+	..	..	..
Harry	+	+	+	+	..	..
Hector	+	+	..	+	++	+
	+				+	
Sophy	+	+	..	+	..	..
	+					
Wiener	+	++	+	..	..	..
Snowball	+	..	+	..	..	..
Tuck	+	+	+	..	..	..
			+			
Terry	+	+	..	+	..	..
Flora	+	+	+	++	++	..
Genevieve	+	+	..	..	..	+
Peter	+	+	+	..	+	+
	+	+	+			
Victor	+	+	..	+	+	+
		+				
Suzy	..	..	..	..	..	..

* The upper crosses indicate lesions in the gray matter; the lower crosses, lesions in the white matter.

TABLE 4.—*Distribution of Lesions in Monkeys Subjected to Anoxia in a Decompression Chamber* *

Monkey	Frontal Lobe	Parietal Lobe	Occipital Lobe	Temporal Lobe	Basal Ganglia	Cerebellum
P61	..	?	..	..	..	..
P64 5	5	7	±	..	+	..
			+			
P65	+	+	+	+	..	..
P66	+	+	+	+	+	+
			+	+		
P67	+	+	+	+	+	+
	+	++	+	+	+	+
P78	+	+	+	+	+	+
	+	++	++	+	+	+
P80	+	+	+	+	..	..
		+				
P81	+	+	+	+	+	+
	++	+++	+	++		
P82	+	+	+	+	++	..
	++	+++	+++	+		
1633	+++	+++	+++	..	++	..

* The upper crosses indicate presence of lesions in the gray matter; the lower crosses, the presence of lesions in the white matter.

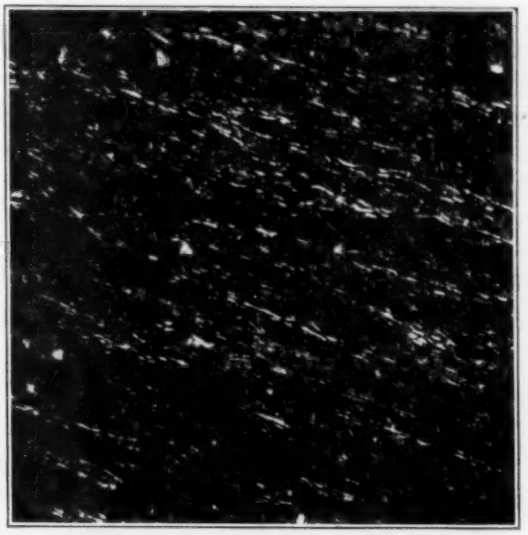

Fig. 26 (monkey P67).—Anisotropic myelin sheaths from pale demyelinated region in serial section next to that from which figure 25 was taken. Oil red O stain; polarized light; × 100.

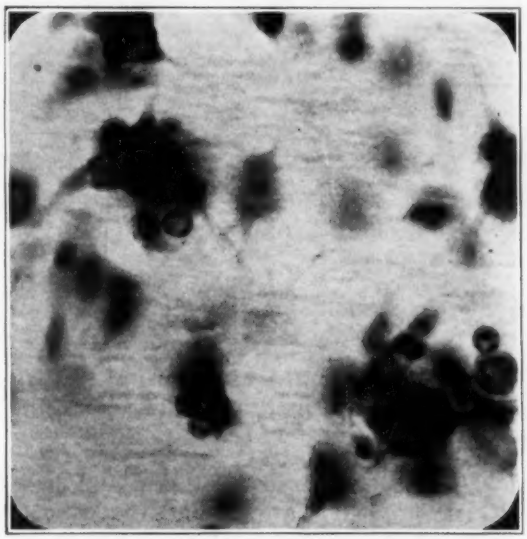

Fig. 27 (monkey P80).—Disease of Betz cells. Swelling and hyperchromatosis in the upper left corner and neuronophagia in the lower right corner. Nissl stain; × 400.

Lesions of the gray matter of the second type were present in 8 of the dogs and in 4 of the monkeys, but not universally so, as one might infer from the literature on acute anoxia. The spinal cord and medulla were the least affected parts of the central nervous system.

The lesions of the white matter were distributed differently. They were present in only 11 of the dogs but were found in all the monkeys but 3, 1 of which (1633) could not be expected to show them. In the monkeys, in which these lesions were present with more regularity, the parietal and occipital lobes were most frequently involved, although the frontal and temporal lobes were not conspicuously unaffected. There was evidently little relation between the presence of lesions of the gray matter and that of lesions of the white matter; the universally affected gray matter of the frontal lobes, for example, was associated with involvement of the white matter in only 9 of the 35 animals.

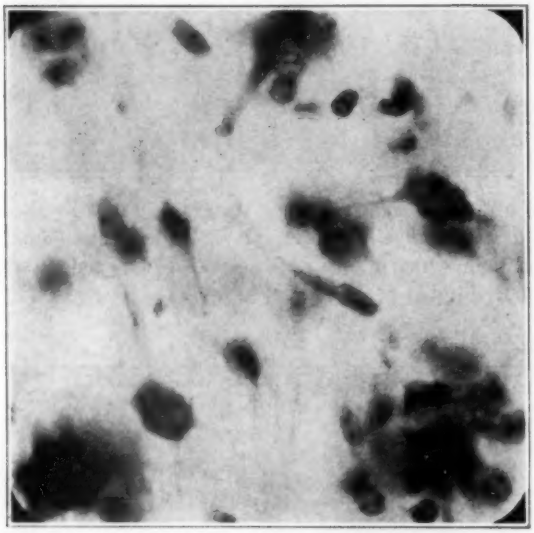

Fig. 28 (monkey P67).—Betz cells with increased number of satellites. Nissl stain; × 400.

Generally speaking, the lesions were bilaterally symmetric in both the gray and the white matter. The lesions of the white matter bore no special relationship to the ventricles and occurred usually in the most central portion of any white matter in which they were present. The first type of lesion of the gray matter, while found almost anywhere in the supragranular layers of any affected lobe, was slightly more common, and probably more intense, over the more exposed surfaces of the gyri than it was in the depths of a buried convolution.

RELATION OF OXYGEN CONTENT OF BLOOD TO DAMAGE TO THE BRAIN

Table 1 shows that the amount of oxygen in the blood of the dogs subjected to various degrees of anoxia varied from 13 to 4.5 volumes per cent, except in the case of 1 dog, which was killed during the first exposure. After the desired oxygen level of the blood was reached, it was kept constant, so far as possible, during any given exposure. The amount of oxygen in the blood of different dogs was kept at different levels during the exposures, but that of each particular dog was kept at the same level each day. On days on which no sample of arterial blood could be obtained, because of hematoma, or for some other reason, the percentage of oxygen in the inspired air, as determined from samples taken from the collecting bag, was used instead as a measurement of the degree of anoxia to which the animal was subjected. Ordinarily, there was a fairly close correlation, in the range at which these experiments were run, between the percentage of oxygen in the inspired air and the volumes per cent of oxygen in the arterial blood.

As has repeatedly been stated, alterations in the ganglion cells of the supragranular layers were the first changes observed from exposures to chronic, intermittent anoxia. At this point the fact is emphasized that individual differences among the animals determined to some extent their tolerance to anoxia. Dog Judith, for example, received 25 exposures at an oxygen level of 13 volumes per cent and presented early lesions in all lobes of the cerebrum, while dog Duncan received 33 exposures at an oxygen level of 12 volumes per cent and had what might be called minimal lesions, and in only the parietal lobe. This was the earliest alteration observed, and, while it would carry more significance if the same number of experiments could have been run on 5 or 6 animals for each oxygen level in order to equalize, more or less, the variation due to individual differences, this oxygen level probably is not far from the threshold at which lesions begin. Assuming that the hemoglobin of dog's blood is similar in combining power to that of human blood, 12 volumes per cent of oxygen in the arterial blood represents, according to Barach and associates,[30] an arterial saturation of about 78.6 per cent. As the oxygen content of the blood reached lower levels, the lesions were found more consistently, provided the number of exposures was great enough. But

30. Barach, A. L.; Brooks, R.; Eckman, M.; Ginsburg, E., and Johnson, A. E.: Appraisal of Tests of Altitude Tolerance, J. Aviation Med. **14**:55, 1943.

dog Oscar, which was subjected to anoxia with an oxygen level of 8 volumes per cent, showed no lesions of any kind, for he had been exposed only four times. Dog Suzy was exposed but once to very severe oxygen deficiency. She was kept for two hours close to the danger threshold (4 volumes per cent or less) and stopped breathing several times, but respiration was started again immediately, with a few breaths of fresh air, and she was then given a low oxygen mixture once more. Two hours after the period of anoxia was begun she died, and the brain presented no alterations which were significant.

Most of these animals presented no untoward clinical signs; and as soon as the gas mask was removed or the animal was taken from the chamber, after two or three minutes of unsteadiness, the dog was apparently recovered, with no reflex abnormalities or other objective signs. But it was difficult to keep the animal alive when the oxygen level of the blood fell much below 4 or 4.5 volumes per cent. Under such conditions breathing would cease, and artificial respiration would have to be used. The dog might then remain unconscious for as long as twenty minutes even though he was breathing air. It

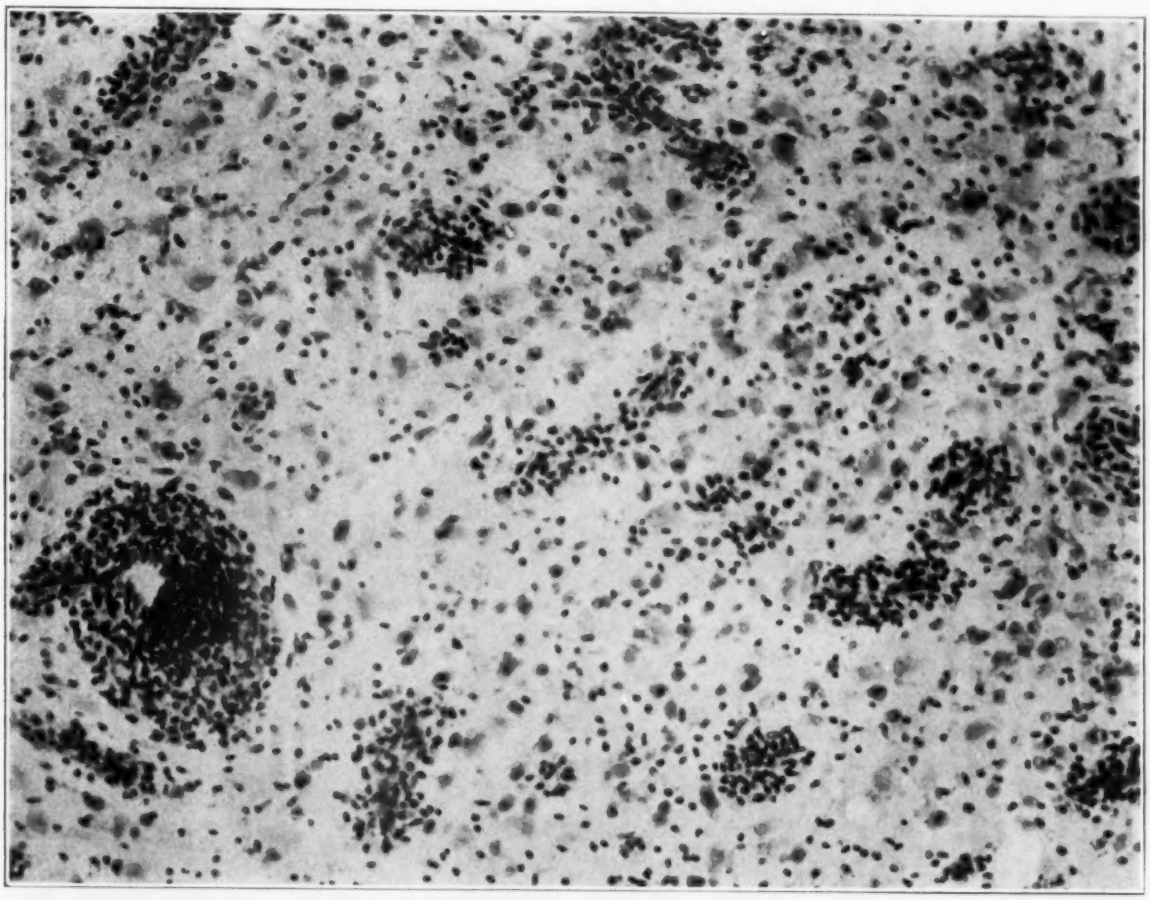

Fig. 29 (monkey P82).—Dense perivascular collars of microglia cells with pleomorphic nuclei. Practically none of these cells was in the gitter cell stage, although this reaction lay in the midst of a focus of demyelination. Nissl stain; × 100.

Here and there a few hyperchromatic cells were seen in the cortex, but no more than one can find in the brain of nearly any control dog. Aside from a certain amount of hyperemia, which one usually encounters in a case of death of this nature, nothing of significance was found. Evidently, two hours is too short a survival time for the production of parenchymatous alterations when the anoxia is not total. This observation is interesting in view of the results reported by Weinberger and the Gibbons,[10] Tureen [9] and Gildea and Cobb.[6]

was in such dogs that the second type of lesion in the gray matter was apt to be found.

The monkeys were exposed in a decompression chamber, and no figures were obtained on the actual oxygen content of the blood. The oxygen content of the atmosphere they breathed was known, however, as well as the barometric pressure, but, presumably, the same correlation did not exist between the oxygen in the inspired air and the oxygen in the blood as was found in the dogs. The monkeys were daily exposed to altitudes of 30,000 feet, where the oxygen in the

atmosphere was the equivalent of about 6 per cent at the pressure at sea level, other things being equal. Such an exposure, however, is more severe than breathing 6 per cent oxygen at sea level. Because of the partial pressures of water vapor and carbon dioxide in the lungs, the equivalent effect is brought down to a plane probably below the effect produced by breathing 4 per cent oxygen at a pressure of 760 mm. of mercury. Judging from the lesions produced in the brain, this is certainly the case; and in considering equivalent altitudes, obviously, not only the oxygen content of the blood but the pressure, as well as other factors with which this investigation is not directly concerned, have to be kept in mind. In the series of 9 monkeys which received repeated exposures, only the first presented no alterations. The second, which was treated in precisely the same way as the first, showed minimal changes in the gray matter. The third, which received three times as many exposures as the first 2 monkeys, and at a slightly higher altitude, showed not only the lesions of the gray matter but the early change in the white matter of type 1. After that, keeping the altitude constant and merely increasing the number of exposures resulted in lesions of both the gray and the white matter in all the remaining monkeys.

REVERSIBILITY OF LESIONS

One dog (Genevieve) was kept alive three months after the last of 33 exposures to anoxia at an oxygen level of about 4.5 volumes per cent. Histologic examination showed that the cerebral cortex still retained many vacuolated, chromatolytic ganglion cells in the outer cortical layers and some shrunken, pyknotic cells elsewhere.

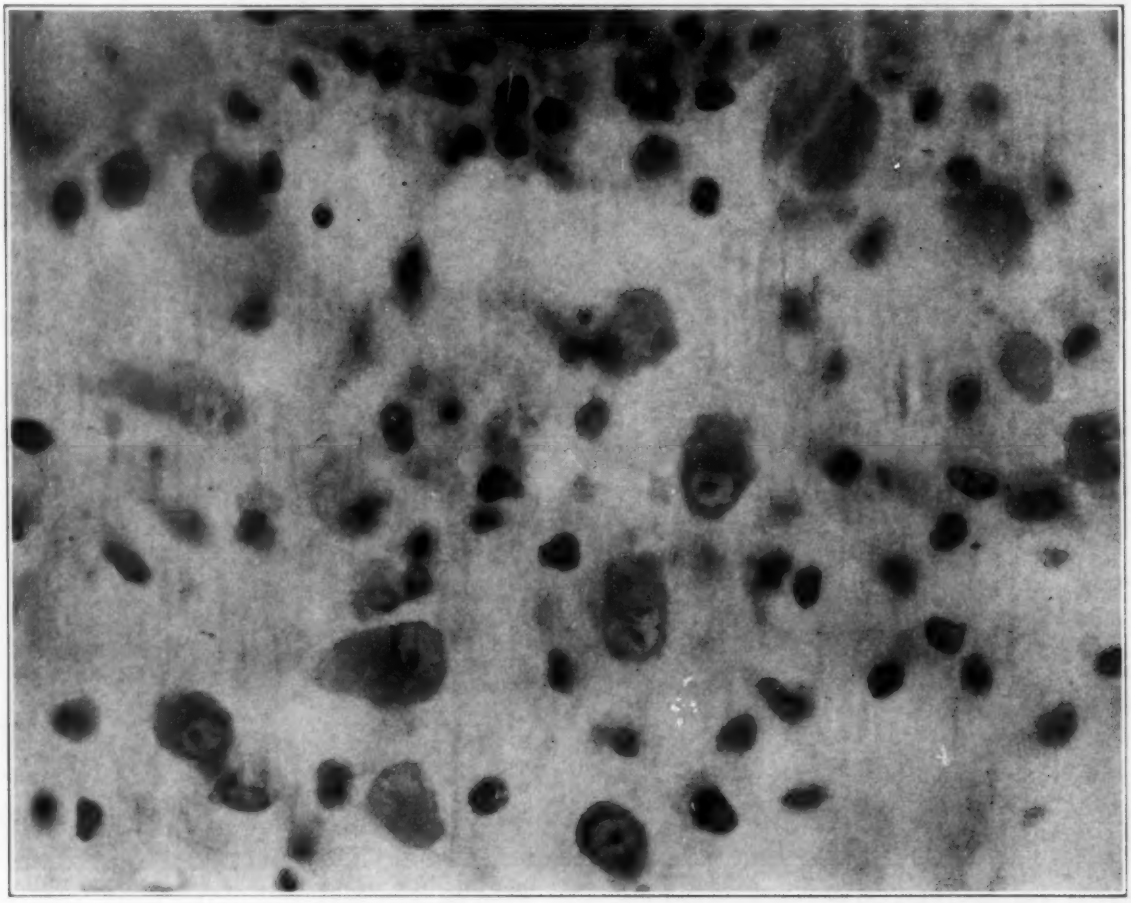

Fig. 30 (monkey P82).—Plump astrocytes in the midst of the microglial reaction shown in figure 29. Nissl stain; × 400.

Interestingly, however, a second dog (Tuck), which had a survival time of six months after having received 39 exposures to anoxia at a level of about 4.5 volumes per cent of oxygen, presented practically none of these vacuolated, swollen, chromatolytic cells. Occasionally a few swollen cells were found in the outer layers, and even more rarely a few vacuoles, but they did not resemble the cells shown in figures 1 and 2. The tigroid substance was even in size, regular in distribution and plentiful in amount. There was no chromatolysis beyond the occa-

sional cell one finds in a control brain. Practically all cells with the "liquefaction" type of degeneration must have reverted to normal.

The shrinkage type of cells also had undergone further changes. There were fewer cells of this type than in dogs with no recovery period, and possibly fewer than in dog Genevieve (the latter comparison has little significance because of individual differences among animals); yet those still present had undergone further change. Some of them were so shrunken as to be scarcely distinguishable from large microglial rod cells. The shrunken, twisted cell body was of the same caliber throughout most of its length. It often lay out of line of the usual cellular architechtonics, showing that its connections were probably interrupted. Other shrunken cells, not so severely diseased, seen especially in the fifth layer, where the larger cells lay, presented streaked Nissl substance and increased numbers of satellites, often in rings. In other words, some of the shrunken cells had reverted to normal; some had gone on to further degeneration, and some were still in the process of reaction, tending probably toward recovery, after the lapse of six months. With regard to the cellular reaction in the lesions in the white matter after six months' survival time, the Holzer stain showed no conspicuous overgrowth of glial fibrils; but distinct hyperplasia of the bodies of astrocytes, with paired daughter cells in abundance, was a feature. The microglial reaction had partially cleared up, for the number of pleomorphic cells was extensive and the number of gitter cells still visible was small. There was no dense microglial cuffing around blood vessels, but the blood vessels themselves had thickened walls not only in the center of lesions of the white matter but, to some extent, in other parts of the brain.

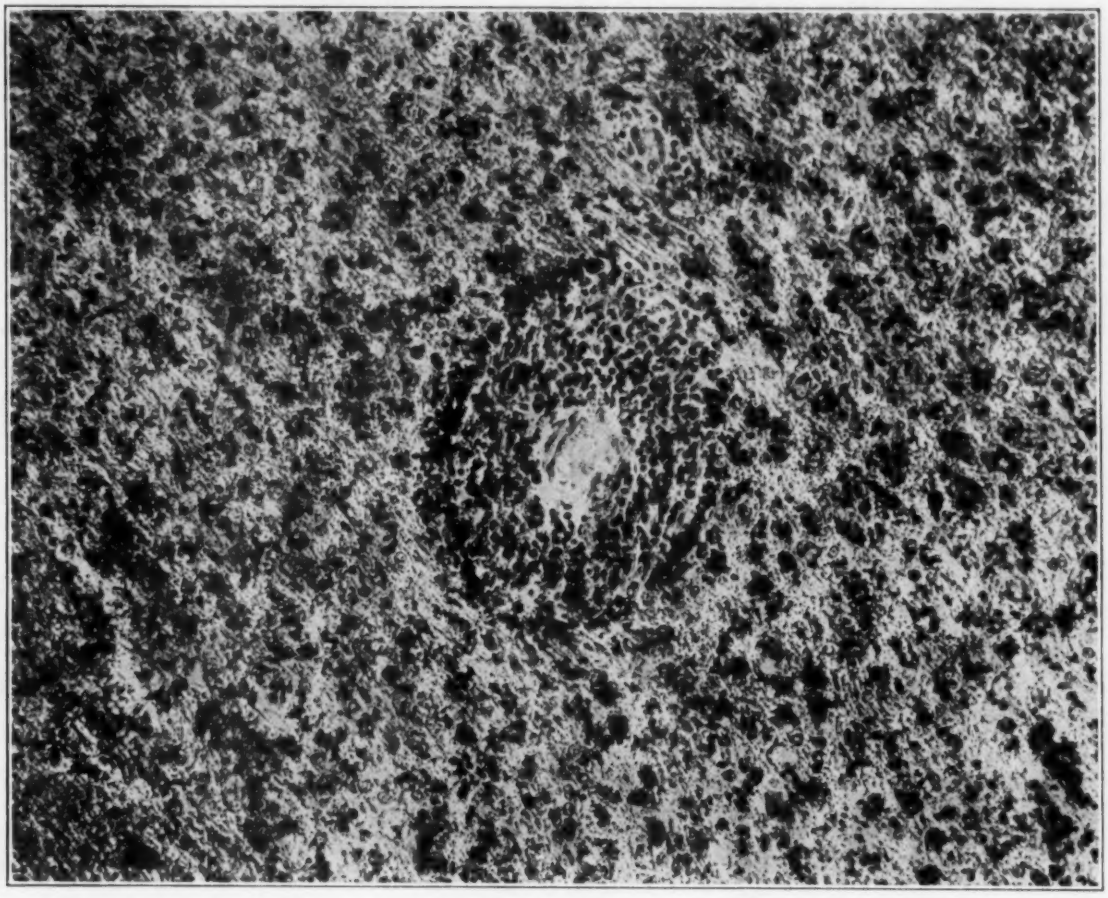

Fig. 31 (monkey P66).—Perivascular cuffing with lymphocytes (and some gitter cells), while beyond the Virchow-Robin space virtually the entire field is composed of fat-laden gitter cells. Oil red O stain; × 100.

GANGLIA OF AUTONOMIC NERVOUS SYSTEM AND ADRENAL GLANDS

Years ago Cannon [31] expressed the view that the sympatheticoadrenal system was involved in the adaptation of the animal to anoxic condi-

31. Cannon, W. B.: Endocrinology and Metabolism, New York, D. Appleton and Company, 1924, vol. 2, p. 174.

tions. Many observations by other workers [32] since that time have confirmed this relationship. It has more recently been reported by Armstrong and Heim [15] that there is hypertrophy of the adrenal glands in conditions of chronic anoxia, and this assertion was later confirmed by Thorn and his co-workers.[33] Ever since the days of Claude Bernard [34] it has been known that anoxia causes glycosuria, and more recently Lewis and associates [33a] have related the increase in sugar in the blood and urine associated with acute anoxia to increased activity of the adrenal cortex. They found, however, that in cases of chronic anoxia hypoglycemia rather than hyperglycemia was present. This observation was in line with the belief expressed by Armstrong and Heim [15] that the adrenal cortex was exhausted in cases of chronic anoxia.

In the present investigation, the adrenal glands were studied histologically, after staining with the phenylhydrazine [22] and oil red O methods, in order to gain, if possible, an idea of the cortical activity. The dogs all weighed between 10 and 12 Kg. The data on the gains in weight of the adrenal glands were not significant, however, because some of the dogs were old and some were young, some were male and some were female and some lost weight during the experiment while others gained weight. The weights of the adrenal glands varied from 0.41 to 1.14 Gm., and no consistent correlation could be found between the larger glands and the severity of the exposures to anoxia. However, if one may

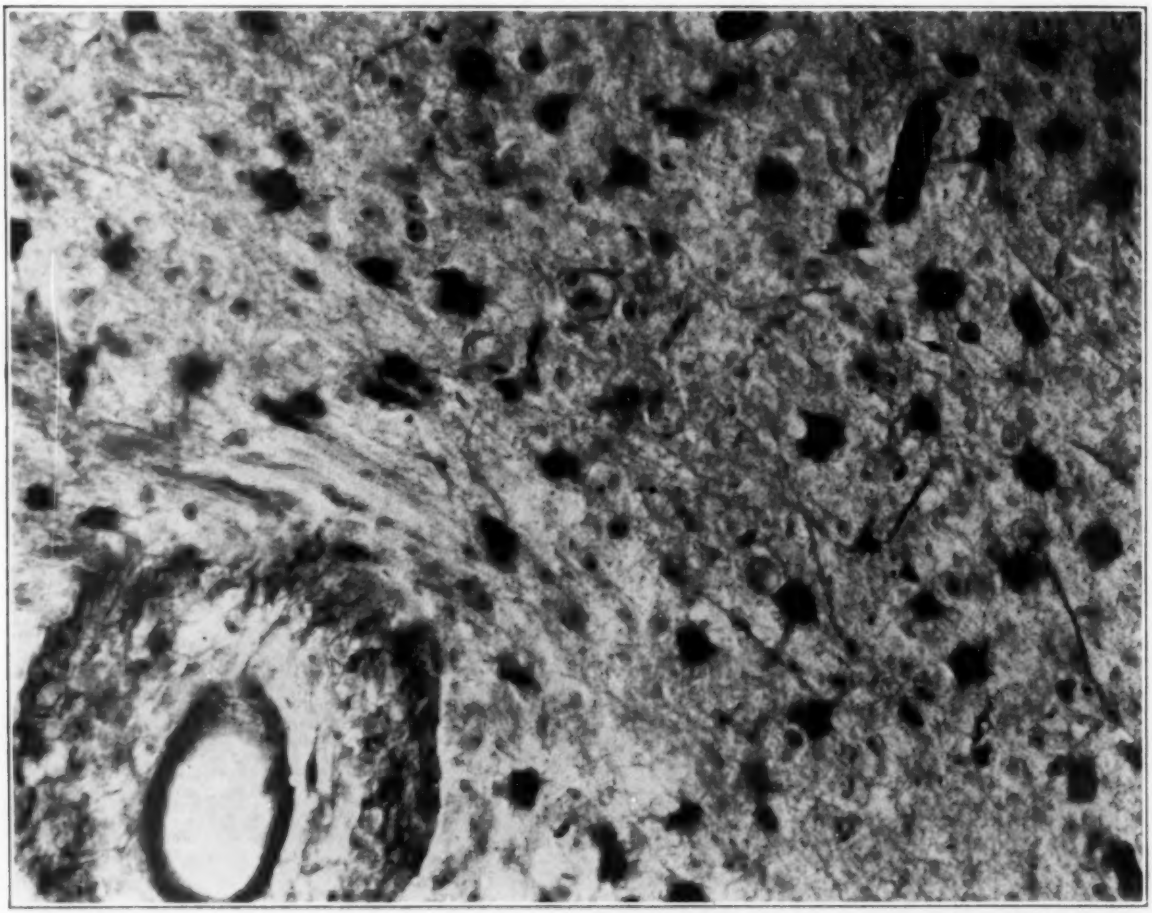

Fig. 32 (monkey P66).—Field in the midst of a focus of demyelination. Astrocytes have lost their processes; oligodendroglia cells are swollen, and the wall of the vessel has hyperplasia of the reticulin. Cajal stain; × 100.

32. Evans, G.: The Effect of Low Atmospheric Pressure on the Glycogen Content of the Rat, Am. J. Physiol. **110**:273, 1934; The Adrenal Cortex and Endogenous Carbohydrate Formation, ibid. **114**:297, 1936.

33. (*a*) Lewis, R. A.; Thorn, G. W.; Koepf, G. F., and Dorrance, S. S.: The Role of the Adrenal Cortex in Acute Anoxia, J. Clin. Investigation **21**:33, 1942. (*b*) Thorn, G. W.; Jones, B. F.; Lewis, R. A.; Mitchell, E. R., and Koepf, G. F.: The Role of the Adrenal Cortex in Anoxia: The Effect of Repeated Daily Exposures to Reduced Oxygen Pressure, Am. J. Physiol. **137**: 606, 1942.

34. Bernard, C.: Leçons sur les effects des substances toxiques et médicamenteuses, Paris, J.-B. Baillière et fils, 1857.

judge from the sections stained with the phenylhydrazine method, there was a degree of activity in the adrenal cortex of the animals with anoxia not present in the normal control. Figure 34 shows a section of cortex of a typical adrenal gland of a dog which had been subjected to chronic anoxia, together with a neighboring section from the same gland after it had been treated with acetone to dissolve the cortical steroids. Figure 35 shows similar sections from a normal dog. It can be seen that greater cortical activity was present in the gland of the anoxic animal. Such activity may have led to

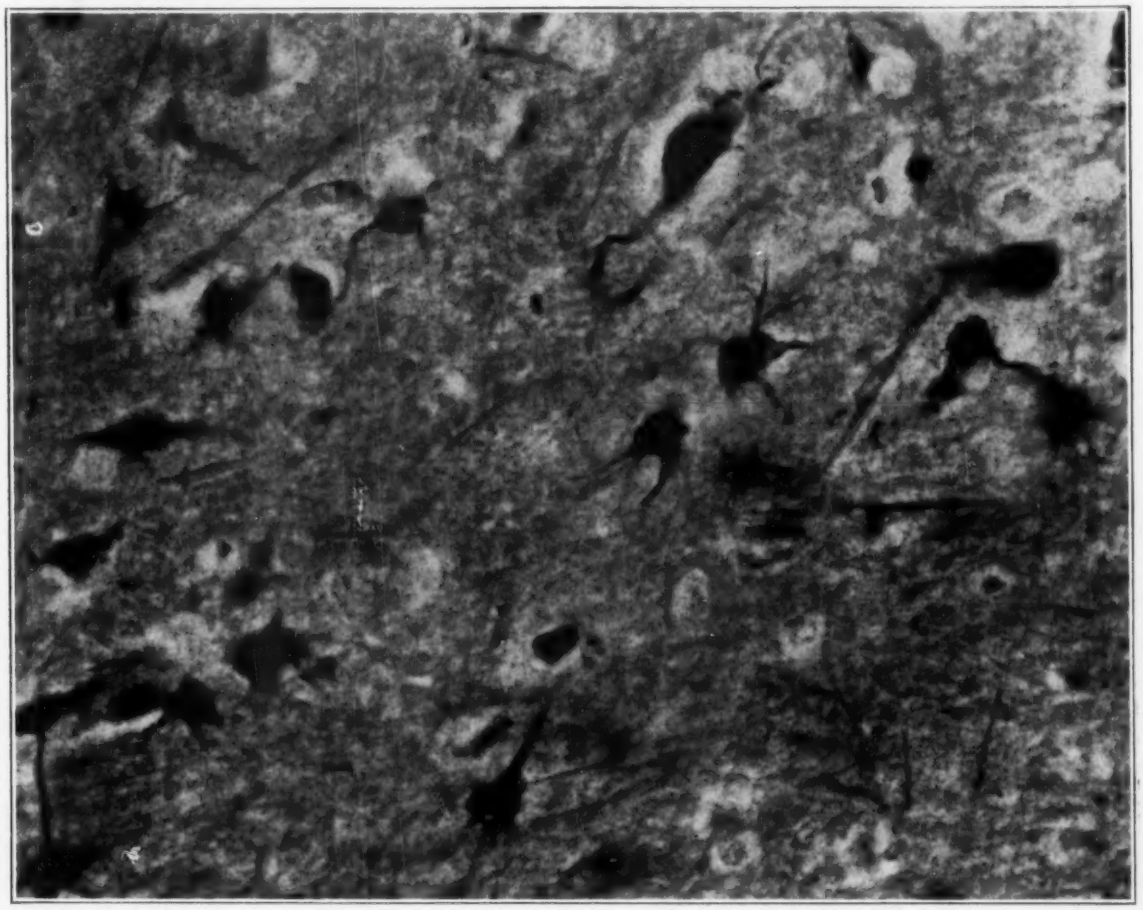

Fig. 33 (monkey P66).—Feeble attempt at astrocytic hyperplasia at edge of the focus seen in figure 32. Cajal stain; × 100.

early exhaustion, and in the hematoxylin and eosin preparation foam cells were often present in the fascicular layer.

The nerve cells of the splanchnic ganglia often showed vacuogranular degeneration but even more frequently presented central chromatolysis with peripheral pyknosis and sometimes complete, or practically complete, lysis of the Nissl substance. In some instances neuronophagia was present, together with increase in capsule cells. No excessive pigmentation was observed. No similar changes were present in the sympathetic cells or in the chromaffin cells of the adrenal medulla, as seen with the cell stain, and no evidence of medullary hypertrophy was at hand.

COMMENT

In the present investigation, even though only one type of oxypenia was produced, practically all the different kinds of lesions were encountered which have been reported by other authors to occur with the various types of anoxia, whether anoxic, anemic, stagnant or histotoxic. The factors which varied, however, were those of time and intensity. Whether the anoxia was acute, subacute or chronic and whether it was mild or severe made considerable difference. In monkey 1633, which was exposed only once but was rather suddenly rushed to a simulated altitude of about 32,000 feet, where it remained for over twenty minutes, and then was permitted to survive for nine days, the damage to the brain was chiefly of the nature of massive laminar cortical necrosis. From the histologic examination it would be impossible to distinguish the lesions in the brain of this monkey from those reported by Courville [5] or by Stewart [27] in cases

of accidental death following nitrous oxide anesthesia. In both instances the anoxia was acute, overwhelming and of short duration; artificial respiration was required before normal breathing recurred and the anoxia was followed by a period of survival sufficiently long to permit the classic reactions to take place. There was, obviously, a hyperplasia of blood vessels with thickening of the vascular walls in the brain of this animal. Courville spoke of an "astrovascular scar" in his cases, but in the case of the monkey the survival time was too short for gliosis to occur. The thick vascular walls, however, presented an interesting reaction. All, or nearly all, the vessels, in addition to a mild fibroblastic or collagenous thickening, had a fairly dense adventitia of reticulin as seen in Perdrau's stain (fig. 20). In the Nissl preparations this reticulin could also be seen, but of course not identified, and with it rows or clusters of oligodendroglia cells. This animal was not the only one in which excessive oligodendroglia cells were found in association with perivascular reticulin, especially among the dogs. Dog Peter (fig. 17) was another such case. While it is true that dogs are more likely to exhibit perivascular oligodendroglia cells than other animals, there seemed to be a relation between reticulin and the oligodendroglia in these animals subjected to anoxia that was closer than one normally finds. Years ago, Penfield,[35] in other circumstances, suggested the possibility of metaplasia of oligodendroglia into rudimentary astrocytes. The "astrovascular scar" in Courville's cases and the hyperplasia of reticulin and oligodendroglia in my animals suggest the interesting thought that there may be a direct relation in the brain between formation of reticulin and the oligodendroglia.

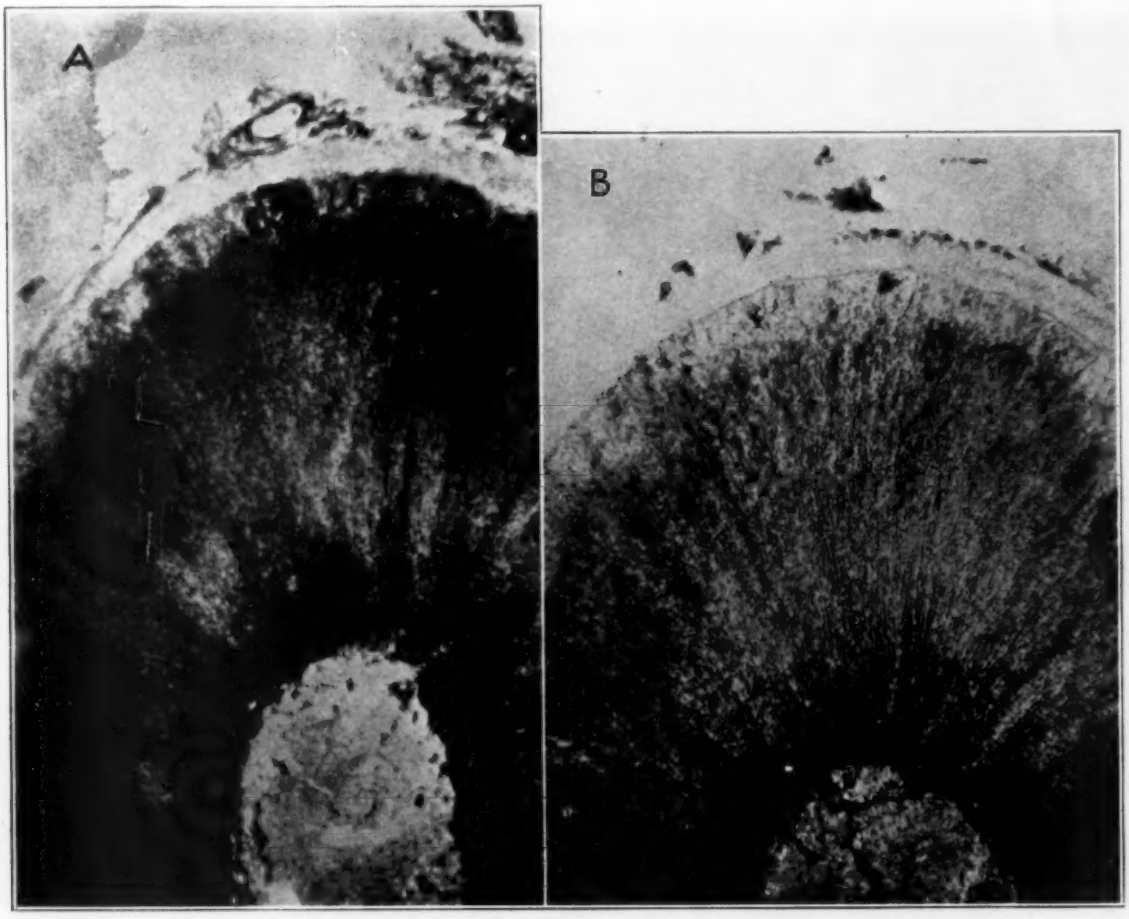

Fig. 34 (dog Timothy).—Adrenal glands stained to show possible cortical activity after daily exposure to anoxia. *A*, test; *B*, control. Phenylhydrazine stain.

In this monkey (1633) there was also a focus of softening in the globus pallidus. Foci of necrosis occurred also in 3 other monkeys and in 6 or 7 dogs. The clinical histories of these animals was usually slightly different from those of the other dogs and monkeys in the experi-

35. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 461.

ment in that they sometimes exhibited signs of an unusual nature. One monkey had a convulsion on one occasion. Another had weakness of the hindlegs. The dogs usually showed no untoward signs, but in several instances it could be seen, in reviewing the protocols, that "accidents" had happened during the experiment. The dog would be breathing along in his usual manner, inhaling the same percentage of oxygen he had formerly breathed without trouble, when suddenly he would stop breathing. After a few seconds or minutes of artificial respiration he would usually breathe normally, although he might remain unconscious several minutes. On one occasion such a dog remained unconscious twenty minutes. On recovery, the animals appeared none the worse, and the experiment was continued. For a few of the dogs, however, the protocols showed no such episodes of unconsciousness and it can only be inferred that exposures to degrees of anoxia down to the level capable of causing necrosis, either complete or incomplete, had been reached without producing clinical signs. There were so many individual differences among the animals, as has been stated repeatedly, that this could very well have happened. In the animals that lost consciousness, however, it was easy to associate, from the point of view of time, the lesion with the episode of unconsciousness. The dog Casper, for example, lost consciousness during the exposure four days before death. On subsequent days he showed no untoward signs. Histologically, his lesions had for their distinguishing characteristic perivascular collections of hematog-

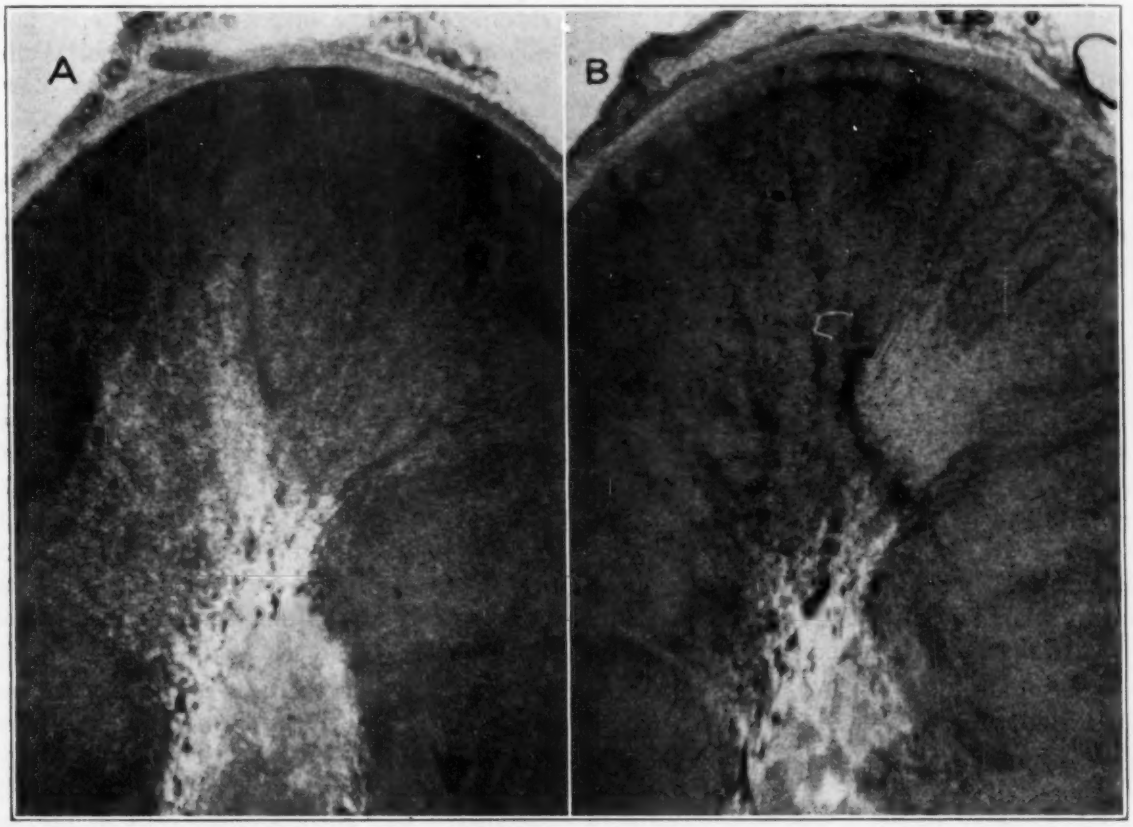

Fig. 35 (control dog).—Animal not exposed to anoxia. *A*, test; *B*, control. Compare with figure 34. Phenylhydrazine stain.

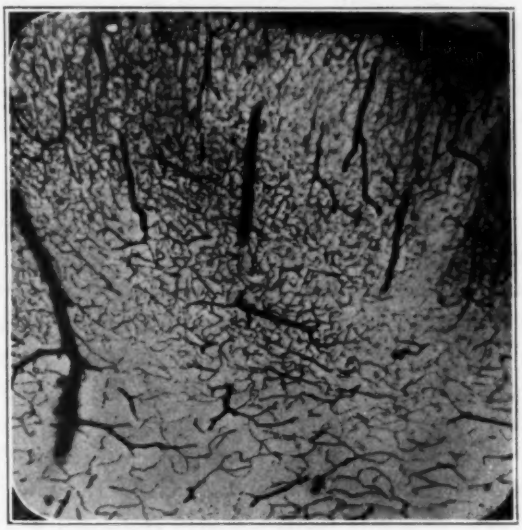

Fig. 36.—Vasodilatation of vessels of the fourth order. Pickworth stain; × 30.

enous cells, chiefly lymphocytes, the presence of which coincided perfectly with the date of loss of consciousness. At the other extreme, monkey P82 had a right-sided convulsion on one occasion two months before death, and pathologically the lesion in his left occipital lobe showed, in addition to advanced necrosis, a streak of old blood pigment and, around the edge, hyperplasia of astrocytes. The lesion in the dog was consistent with a four day reaction, and that in the monkey, with a two month reaction.

Here, too, the method of producing the anoxia seems important. In monkey 1633 the anoxia was overwhelming (for that particular animal, although another animal might have withstood it) and the induction fairly sudden, and anoxia so produced could also account for the accidents occurring during nitrous oxide anesthesia. With the other monkeys and dogs of this group, however, the circumstances were rather different. These animals had been subjected to anoxia before, usually many times, and on the date of loss of consciousness—if they lost it—the oxygen had been running along rather close to the danger threshold, possibly for some hours, and had only gradually slipped over into that degree of anoxia incompatible with the life of brain tissue. They were immediately given pure air to breathe; so the actual duration of the dangerous level of anoxia, even though it may have been preceded by several hours of severe anoxia, was probably very brief. Both these types of lesions, however, were the result of acute episodes of severe anoxia, whether or not they occurred in the midst of exposures of relatively mild anoxia of longer duration.

That anoxia of a degree sufficiently intense to cause convulsions need not be long enough or complete enough to cause necrosis was shown by Gildea and Cobb[6] in their ligation experiments. On the other hand, necrosis can certainly be produced by acute ligation experiments, as was recently shown by Weinberger and the Gibbons.[10] By the same mechanism, thrombosis, so often found in cases of carbon monoxide poisoning,[7] could easily explain much of the necrosis associated with that type of anoxia. But in the present experiment no thrombi were found, even though in several of the dogs, such as Peter and Hector, lesions were present in the thalamus which were bilaterally symmetric. Whether these thalamic lesions were produced by temporary vasoconstriction (ischemic necrosis), whether the thalamus was locus minoris resistenti to low degree of oxygen saturation of the blood or whether vasodilatation to the point of stasis occurred is not known; at any rate, the thalamus was the most common site of the second type of lesion of the gray matter in the dogs.

The first type of lesion of the gray matter, which was concerned chiefly with alterations in the nerve cells, was the earliest and most consistently encountered abnormality. The swelling, chromatolysis and vacuolation of the cells in the supragranular layers, as well as the ischemic and chronic shrinkage in cells in the deeper layers, might be considered early physicochemical alterations, as suggested by Thorner and Lewy,[16] rather than "true degenerative changes." But such a distinction is obviously arbitrary, for severe degenerations, too, must be physicochemical. The question is one of degree and of reversibility.

The cytoplasm of some of the shrunken cells took a pink color with hematoxylin and eosin; and when silver preparations were made, cell bodies stood out prominently in regions where only nuclei or ghost cells could be seen with the Nissl stain. Such alterations were probably often reversible, for in the 2 dogs with long survival periods such *Herde* were not seen frequently and, while there were still some cells with pronounced so-called chronic shrinkage, their number was rather small and the number of ischemic cells was insignificant.

With regard to the cells of the supergranular layers, however, the problem was slightly more difficult. At least 1 of the 5 control dogs presented a fairly conspicuous number of swollen, vacuolated and chromatolytic cells in the same outer cortical layers. In the other control dogs, also, at least occasional cells of this type could be found, although no other pathologic change and no history or sign of disease could be obtained. One great difference, however, between the animals exposed to anoxia and the controls was the difference in intensity of this type of reaction, the change being much milder even in the most conspicuously affected control. The other difference was in the quality of the lesion. In the exposed dogs, there was a distinct pulverization of the tigroid substance, and true vacuoles were present in the cytoplasm. In the control dogs, this change was more apparent than real, for the large "vacuoles," which separated the cell membrane by a considerable distance from the rest of the cell body, gave the appearance of pseudoedematous swelling of the perikaryon. The condition resembled the artefacts often produced in paraffin sections or many of those "vacuoles," for example, called "lique-

faction necrosis" in the work of Chornyak,[36] in which acetic acid was used in the fixative.

Since fat was practically never present in these cells, it may be inferred that they, too, had undergone only the first stages of "physicochemical" change. This was a reversible lesion, to a large extent, because, after months of recovery not many of these supragranular cells showed any traces of swelling, chromatolysis or vacuolation.

One reason that these cells were not engulfed by satellites during the weeks of their abnormal condition may be that the glia also experienced these edematous changes. Figure 3 *B* shows swollen oligodendroglia cells among the swollen, vacuolated nerve cells; although swelling of oligodendroglia cells may be a reversible reaction, it probably precludes hyperplasia or any further adsorptive activity on the part of those cells while they remain in a swollen condition.

The most common effect on the cerebral circulation of a diminished oxygen supply of the blood is vasodilatation. This may go on to the point of stasis. Stasis in the larger vessels of the fourth order[37] penetrating the supragranular layers on their way to the depths of the brain may well give rise to edema. In fact, edema of the brain in cases of anoxia has been reported by many authors.[38] The smaller caliber of the vessels (arterioles) and the less extensive capillary bed in the deeper cortical layers may account for better vasomotor tone, with the result that shrinkage rather than swelling was the response of the nerve cells observed. Preparations with the methods of Pickworth and of Eros were made of some of the dog brains (fig. 36), but it was early apparent that if they showed anything significant it was merely the state of the blood vessels at the time of death. No conclusions could be drawn with regard to the state of the vessels during life; and if the dogs were killed by intravenous injection of pentobarbital twenty-four hours or so after their last exposure to anoxia, as they were, for other reasons, little could be inferred regarding the state of the blood vessels during anoxia. It is felt that far too much emphasis is placed on this technic by certain authors.[37]

Another point must be considered in discussing the alterations in the supragranular layers, namely, fatigue of the nerve cell. The sequence of changes produced in nerve cells by fatigue has been worked out by Dolley,[39] Mann [40] and others.[41] That nerve cells are stimulated to increased activity by anoxia is common knowledge.[42] In the present experiment, in which nerve cells were exposed for four hours daily to severe oxygen want, the cells in the association layers presented the picture of almost complete exhaustion—swelling of the cell body and of the nucleus and virtual absence of Nissl substance. In the deeper layers, where the process was less severe, degrees of this exhaustion picture could be found: smaller cells; darkly staining Nissl substance about the periphery, especially in the ischemic cells; chromatolysis throughout the rest of the cytoplasm; a dark ring of chromatin about the nucleus; often dark nucleoplasm, and a gearlike irregularity of the nucleolus. These may all be different stages of fatigue, according to the aforementioned authors, and they were found in abundance throughout the brain in this study, not only in the cortex but in the basal ganglia. Unfortunately, the amount of oxygen in the arterial blood tells little regarding cellular anoxia,[43] and while there may not have been enough anoxia over such a widespread area to cause the reaction of infarction that was discussed in connection with the production of the second type of lesion in the gray matter, there may have been sufficient lack of oxygen to cause all degrees of nerve cell exhaustion. Then, the fact that this anoxia was repeated, day after day, may have had an effect just noxious enough to keep the nerve cells from recuperating. The combination of fatigue and anoxia, if indeed they are not the same thing, with reference to these nerve cells, may

36. Chornyak, J.: The Structural Changes Produced in the Human Brain by Oxygen Deprivation (Anoxemia) and Their Pathogenesis, Ann Arbor, Mich., Edwards Brothers, Inc., 1938, p. 77.

37. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**: 471, 1938.

38. Gildea and Cobb.[6] Ferraro and Morrison.[7] Chornyak.[36]

39. Dolley, D. H.: Morphological Changes in Nerve Cells Resulting from Overwork in Relation to Experimental Anemia and Shock, J. M. Research **16**:95 and 309, 1909; Studies on the Recuperation of Nerve Cells After Functional Activity from Youth to Senility, ibid. **19**:309, 1911.

40. Mann, G.: Histological Changes Induced in Sympathetic, Motor and Sensory Nerve Cells by Functional Activity, J. Anat. & Physiol. **29**:100, 1895.

41. Eve, F. C.: Sympathetic Nerve Cells and Their Basophil Constituent in Prolonged Activity and Repose, J. Physiol. **20**:334, 1896. Hodge, C. F.: A Microscopical Study of Changes Due to Functional Activity of Nerve Cells, J. Morphol. **7**:95, 1892. Ingersoll, E. H.: The Effect of Stimulation upon the Coeliac Ganglion Cells of the Albino Rat, J. Comp. Neurol. **59**: 267, 1934.

42. Landis, E. M.: Micro-Injection Studies of Capillary Permeability, Am. J. Physiol. **83**: 528, 1928.

43. Hartman, F. W.: Some Etiological Factors and Lesions in Anoxia, Am. J. Clin. Path. **8**:629, 1938.

have brought about these changes independently of vasomotor conditions. Regardless of the precise physiologic mechanism by which these cell changes were produced, they were the result of anoxia that was chronic, intermittent and not sufficiently severe to produce infarction in the cortical regions. One believes the repetitive effect of this type of anoxia is important in producing lesions that a single exposure or a few exposures would not produce.

A further accentuation of the effect of this chronic, intermittent oxypenia was seen in the lesions of the white matter. While the nerve cell bodies were affected by relatively low degrees of anoxia, or by exposure to somewhat lesser degrees of anoxia repeated a greater number of times, the white matter was not, as a general thing, involved until the anoxia was even greater or the number of exposures was even higher. This lesion of the white matter was an almost unique response and, so far as can be ascertained, has not been reported by any of the many previous workers on anoxia except Ferraro [13] and, later, Hurst,[14] who found it while working on experimental demyelination produced by potassium cyanide. It is probable that the reaction they produced in the white matter was brought about by histotoxic anoxia acting, as Hurst suggested, by the interruption of one, or several, of the enzyme system reactions within the brain. At any rate, as far as experiments to produce demyelination are concerned, those in which potassium cyanide or sodium azide and the like were used are the only ones that gave consistent results. As far as anoxia is concerned, in its relation to demyelination, the technic used in the present investigation, also, gave consistent results. The chief factor which these two types of experiments had in common was the repetition of daily, sublethal doses over a sufficiently long time. Evidently, the constant repetition is essential in the production of these lesions. Since the action of cyanide is evanescent—it does not accumulate in the body—and the action of simple anoxic anoxia is likewise transient in its effects, a few breaths of fresh air relieving the anoxia, the disease of the myelin must have been the result, not of the cumulative effect of either the drug or the anoxia, but, rather, of the ultimate irreversibility of physiologic reactions that were in the intervening, recuperative hours of the early days of the experiments very largely reversible. Rather than to consider the loss of myelin a specific action of anoxia on the white matter, it seems more reasonable to assume, with Hurst, that demyelination is a "type of response" to a series of episodes of anoxia no one of which would have, in itself, been capable of producing changes that were irreversible. It is true that Hurst had 1 monkey which showed demyelination after thirty hours, and there was 1 dog in the present study that presented early loss of myelin in eleven days, after exposure to fairly mild anoxia; but it is emphasized again that all animals do not react in the same way. However, in general, it may be said that it takes a fairly long series of exposures to a degree of anoxia which in a single exposure would be incapable of causing destruction to produce these lesions of the white matter. The fact that cyanide is a potent enzyme inhibitor, in all probability, explains the demyelination produced by its daily use by Ferraro and by Hurst. The production of similar lesions in the present investigation by the method of daily exposures to anoxic anoxia does not necessarily imply a similar interruption of enzyme system reactions, although it does not preclude it. The same final effect may result from want of oxygen produced in either way. Yet even in the present study, the chronic, intermittent nature of the exposures, coupled with the fact that the cerebral metabolism was presumably swinging back and forth between the aerobic and the anaerobic type, may well after a while have interrupted the normal enzyme system reactions.

The nature of the medullary lesions seen here was not quite the same as that of the lesions reported by Hurst. This may have been due to difference in technic in producing them or to difference in severity of the anoxia, or even to difference in survival time after they were produced. The chief distinction was that in no instance was a peripheral reaction of histologic elements found in this investigation. Hurst was able to "date" his lesions by the glial response at the periphery. In the present study when there was a glial reaction it was in the more central portions of the lesion, usually, or at least often, around a blood vessel or a series of blood vessels. In the earliest type of lesion of the white matter no glial response was present, there being merely a blanching of the white matter in the myelin preparations. This alteration of the myelin was followed by hyperplasia of pleomorphic microglia cells in the depths of the lesion. The microglia cells became normal in number and shape as the edge of the lesion was reached. This was in line with the observation of Bodian and Howe,[44] in

44. Bodian, D., and Howe, H. A.: Neural Mechanisms in Poliomyelitis, New York, Commonwealth Fund, 1942, p. 233.

other circumstances, in which they presented the idea that microglia cells do not proliferate in the presence of virus (poliomyelitis) but, rather, that they become hyperplastic only after the nerve cells have been damaged; that is, the hyperplasia of microglia in virus diseases is a response to injured nerve tissue rather than a response to virus. The same situation obtains in the present experiment; the microglia responded to the injured myelin rather than to anoxia or to some other influence. In other words, demyelination was seen first; the microglial response followed. There were 1 or 2 cases in which a single slight cluster of perivascular microglia cells was present with no obvious demyelination, but it was felt that since it was not quite typical of the other microglial reactions it ought to be overlooked. Besides, the demyelination, which in the early stages was not always easy to bring out, may have been missed, through a technical fault.

As stated in the body of the paper, the more central parts of these demyelinated patches sometimes showed fatty necrosis; i.e., the lesion was older in the center than it was on the edge. The microglia had become fat-laden gitter cells, and the anisotropic myelin had lost its double refractility, had taken the stains for fat and presented the conventional myelin figures. Much of this fat was scattered throughout the focus, but some of it was accumulated, in the conventional places, in the Virchow-Robin spaces and in the fibroblasts of the walls of blood vessels, whence it probably went into solution in excess of fatty acid, as Leary [45] showed in the case of cholesterol, and thence into the blood stream. Not only did the gitter cells pick up neutral fat in their well known phagocytosing, but in some instances they extended their Abbau activity to anisotropic myelin.

There was not much reaction to the Holzer stain in the brains of any of the animals, as if gliosis were to take an inordinately long time if, indeed, it were going to occur at all. With the Cajal and Nissl stains some evidence of astrocytic hyperplasia was to be seen, as previously stated, but caution must be exercised in attributing any degree of age to the presence of plump astrocytes. It is true these cells are usually seen in a chronic process, but they certainly also occur acutely, since they were present in abundance in monkey 1633, which had but a nine day survival time. Some of the monkeys with severe demyelination died at altitude or were killed fairly early, after 40 or 50 exposures to anoxia, while others that were exposed to the same degree of anoxia for twice that length of time presumably had lesions as soon as the former. Yet the amount of gliosis was not much greater in the latter group.

It is interesting to point out that this is not the only type of anoxia with which frank gliosis failed to occur. In monkeys that were exposed to chronic, intermittent insulin shocks, Finley and Brenner [46] were able to find signs of astrocytic hyperplasia but no distinct glial scars. Weil and associates [47] and Tannenberg [48] obtained similar results.

Regardless of whether or not the metabolism of glucose in the brain is dependent on the action of insulin,[49] insulin shock rids the brain of glucose and consequently halts metabolism. During anoxia, in an effort to compensate for the lack of oxygen, the organism attempts to produce more glucose; hence the hyperglycemia associated with acute anoxia.[50] Thorn and associates [33b] showed that this extra sugar comes from protein through increased activity of the adrenal cortex; there was increased adrenal cortical activity in the present experiment (fig. 34). Whether anaerobic glycolysis accounts for the absence of increased glycogen in the brain associated with anoxia is not known,[51] but there was no increase in these animals. This fits in well with the rest of the observations. If the animals had had plenty of glucose in the brain, as there presumably is with various forms of acute anoxia, it might not have been possible to

45. Leary, T.: Cholesterol Lysis in Atheroma, Arch. Path. **37**:16 (Jan.) 1944.

46. Finley, K. H., and Brenner, C.: Histologic Evidence of Damage to Brain in Monkeys Treated with Metrazol and Insulin, Arch. Neurol. & Psychiat. **45**:403 (March) 1941.

47. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

48. Tannenberg, J.: Comparative Experimental Studies on Symptomatology and Anatomical Changes Produced by Anoxic and Insulin Shock, Proc. Soc. Exper. Biol. & Med. **40**:94, 1939.

49. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938.

50. Kellaway, C. H.: Hyperglycemia of Asphyxia and Part Played Therein by Suprarenals, J. Physiol. **53**:211, 1919. Bernard.[34]

51. Holmes, B. E., and Holmes, E. G.: Contributions to Study of Brain Metabolism, Biochem. J. **19**:351, 1925; Carbohydrate Metabolism: Preliminary Paper, ibid. **19**:492, 1925; Carbohydrate Metabolism, ibid. **19**: 836, 1925; Study of Brain Metabolism: Carbohydrate Metabolism of Brain Tissue of Depancreatised Cats, ibid. **21**:412, 1927. Holmes, E. G., and Holmes, B. E.: A Note on the Reducing Substances Found in Alcoholic Extracts of Brain, ibid. **20**:595, 1926. Holmes, B. E., and Holmes, E. G.: Study of Brain Metabolism: Carbohydrate Metabolism; Relationship of Glycogen and Lactic Acid, ibid. **20**:1196, 1926.

produce this new type of lesion in the white matter. The oxidation systems in the brain were probably interfered with irreparably by the absence of both glucose and oxygen.

SUMMARY

Twenty-five dogs were exposed daily to atmospheres of low oxygen concentration at the pressure of sea level and 10 monkeys were similarly exposed in a decompression chamber. The oxygen content of the arterial blood was measured in the dogs. Histologic studies were made on the central nervous systems of all the animals and on the adrenal glands of the dogs.

The degree and duration of anoxia were important.

It was found that a single, sudden exposure to a simulated altitude of 32,000 feet (10,000 meters) for twenty-five minutes was capable of producing extensive laminar necrosis in the cortex of the monkey.

With repeated exposures to mild hypoxia, it was observed that the first histologic changes occurred in the cell bodies of the cortical gray matter. This took place at a level of about 12 or 13 volumes per cent of oxygen in the blood if the exposures were long enough and were repeated often enough.

When the percentage of oxygen was reduced still lower, to about 10 volumes per cent, and the number of exposures was increased, the white matter also became involved and presented a pattern of demyelination in the corpus callosum, the centrum semiovale and the adjacent fingers of subcortical white matter which, in the cases of more severe anoxia, suggested a resemblance to Schilder's disease.

Aside from the lesion of the white matter, frank necrosis was usually found to occur only after episodes of anoxia sufficiently severe to produce cessation of respiration.

The frontal lobe was most often involved and the temporal lobe least often. The cerebellum was more frequently affected than the basal ganglia, and the spinal cord and medulla were unaffected by any degree of anoxia compatible with life. An oxygen level of 4, or 4.5 volumes per cent was about as low as a dog could tolerate. Respirations quickly ceased below that level.

The adrenal glands showed increased cortical activity.

Dr. Stanley Cobb offered valuable suggestions, and Miss Margaret Carroll and Miss Ruth Harwood gave technical assistance.

Massachusetts General Hospital.

NEUROLOGIC MANIFESTATIONS ASSOCIATED WITH MALARIA IN DUCKS

A CLINICOPATHOLOGIC STUDY

D. E. FLETCHER, PH.D., AND R. H. RIGDON, M.D.
LITTLE ROCK, ARK.

That persons with malaria often show symptoms suggesting involvement of the nervous system has been recognized for many years. However, recently there has been an increase of interest in regard to these neurologic manifestations associated with malarial infections. Harvey,[1] in 1944, reported several cases of malaria with associated neuritis. Fitz-Hugh and associates,[2] in 1945, presented a large series of cases of malaria in which there was cerebral involvement. McGinn and Carmody,[3] in 1944, observed that "at a base hospital, cerebral symptoms have been the most serious and frequent complication in patients suffering from malaria." Kean and Smith[4] reviewed 100 cases of estivo-autumnal malaria with autopsy and concluded that "the plugging of cerebral capillaries did not appear to be closely related to the occurrence of the symptoms of cerebral malaria." One of us (R. H. R.),[5] in 1944, reviewed the lesions in the brain occurring with malaria and discussed their pathogenesis. Dhayagude and Purandare,[6] in 1943, described the lesions of cerebral malaria, giving special attention to the malarial granulomas. We[7] recently described the pathologic changes in the brain of a child infected with Plasmodium falciparum and in the brains of monkeys infected with Plasmodium knowlesi and discussed their pathogenesis. We also included in our study the acute lesions occurring in the cerebellum of chicks and ducks infected with Plasmodium lophurae.

The present paper considers the clinical manifestation observed in a large series of white Pekin ducks infected with malaria and describes the associated pathologic changes which were found in the nervous system of 26 of these birds.[8]

CLINICAL OBSERVATIONS

The ducks used in this study were inoculated intravenously with P. lophurae, and a majority of them died of the infection before the tenth day. In these birds a severe anemia rapidly developed. The red blood cell count frequently decreased from the normal, of 2,500,000, to 500,000, per cubic millimeter, during the acute phase of the infection. The degree of parasitemia was determined by counting the number of parasitized cells per 500 red blood cells. In fatal cases, 450 parasitized cells per 500 red blood cells were frequently found.

The severely infected ducks became pale and weak, and within a few hours preceding death they took neither food nor water. One or more convulsions usually occurred before death.

Older birds given an injection of an inoculum containing fewer parasites were more likely to survive the acute infection. After the crisis was passed these ducks rapidly recovered from their anemia. The malarial parasites disappeared completely from the circulating blood, and then these ducks could not be distinguished from the normal controls.

From the Department of Pathology, University of Arkansas School of Medicine.

This study was aided by grants from the John and Mary R. Markle Foundation and Eli Lilly and Company.

1. Harvey, A. M.: A Type of Neuritis Associated with Malarial Fever, Bull. Johns Hopkins Hosp. **75**: 225-231, 1944.

2. Fitz-Hugh, T., Jr.; Pepper, D. S., and Hopkins, H. U.: The Cerebral Form of Malaria, Bull. U. S. Army M. Dept., 1944, no. 83, pp. 39-48; abstracted, Trop. Dis. Bull. **42**:340, 1945.

3. McGinn, S., and Carmody, J. T. B.: Cerebral Symptoms in Malaria, U. S. Nav. M. Bull. **43**:1157-1162, 1944; abstracted, Trop. Dis. Bull. **42**:341, 1945.

4. Kean, B. H., and Smith, J. A.: Death Due to Estivo-Autumnal Malaria: A Résumé of One Hundred Autopsy Cases, 1925 to 1942, Am. J. Trop. Med. **24**: 317-322, 1944.

5. Rigdon, R. H.: The Pathological Lesions in the Brain in Malaria, South. M. J. **37**:687-694, 1944.

6. Dhayagude, R. G., and Purandare, N. M.: Autopsy Study of Cerebral Malaria with Special Reference to the Malarial Granuloma, Arch. Path. **36**:550-558 (Dec.) 1943.

7. Rigdon, R. H., and Fletcher, D. E.: Lesions in the Brain Associated with Malaria: Pathologic Study on Man and on Experimental Animals, Arch. Neurol. & Psychiat. **53**:191-198 (March) 1945.

8. Five ducks showing neurologic manifestations were contributed to this study by Mr. E. R. Rose, of Eli Lilly and Company.

However, within a period of two to six weeks after inoculation, a majority of the ducks which had recovered from the malarial infection had neurologic manifestations. A disturbance in locomotion and gait was the first change observed. These ducks showed reduced volitional activity. They moved slowly, lifted their feet in high steps and slapped them forcibly on the floor. They maintained a broad stance, rocked to and fro and occasionally fell forward on the breast or backward on the tail. When forced to move at a rapid rate, the affected ducks extended either the right or the left wing in order to prevent falling to that side.

The neurologic manifestations of disturbance in equilibrium and locomotion became exaggerated when the ducks were blindfolded. Furthermore, they were unable to remove the blindfold by scratching. The flexed foot, instead of reaching the blindfold, was thrust away from the head with force sufficient to pivot the bird on its breast. These movements of alternate flexion and extension were slowly, awkwardly and ineffectively performed.

None of the ducks showed evidence of paralysis. But they moved with a characteristic stiffness, and a mild degree of rigidity was present when the legs were passively moved.

The ducks with the neurologic manifestations were killed at varying intervals except for a few that made a complete, spontaneous recovery. The symptoms in these birds persisted for two to four weeks, during which time they gradually receded. After recovery from the neurologic disturbances the ducks could not be distinguished from the controls.

A majority of the birds used in this study were killed at various intervals during and after the infection by clamping the neck and immediately removing and fixing the brain. Noninfected ducks were similarly killed to serve as controls. A few birds were permitted to die of the disease, and their brains were removed immediately for study.

PATHOLOGIC OBSERVATIONS

In the ducks which showed a high degree of parasitemia, edema, generalized vascular congestion and stasis were present throughout the brain and the spinal cord. In tissues fixed either in Bouin's solution or in solution of formaldehyde U. S. P. diluted 1 to 10 and stained with hematoxylin and eosin, the capillaries and venules were dilated, the endothelial cells were swollen and the walls of vessels were edematous. The perivascular spaces were enlarged, and the surrounding nerve tissue was pale staining and reticulated. Occasionally petechiae were present.

In the cerebral hemispheres, the nerve cells showed early degenerative changes. In hematoxylin and eosin and thionine preparations many

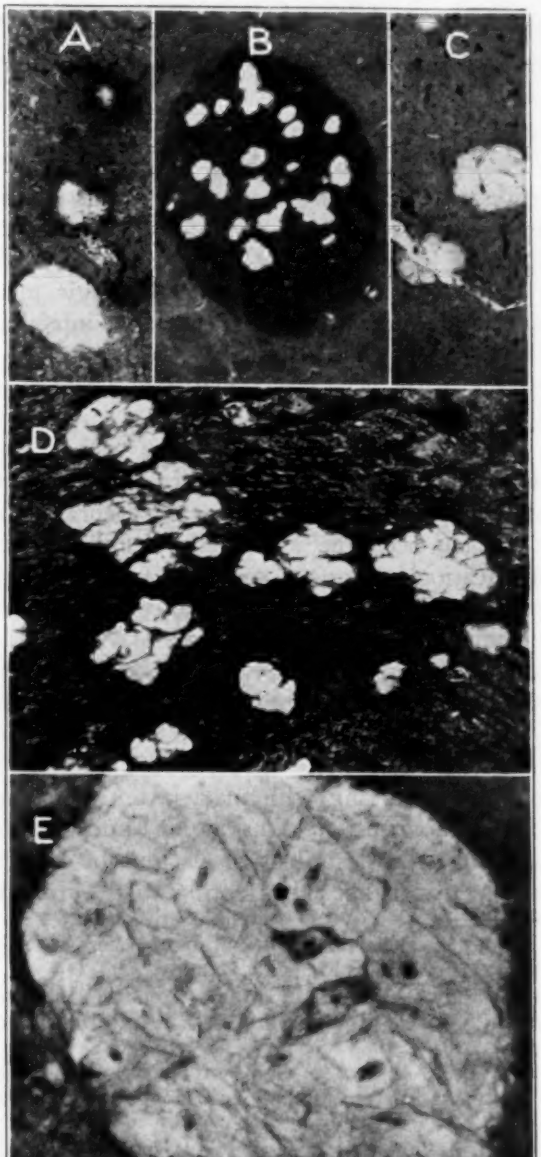

Fig. 1.—Focal lesions in the brain of ducks infected with P. lophurae. (*A*) These lesions first appear as darkly stained areas, which gradually expand into large vesicular, fluid-filled spaces. (*B*) Multiple lesions in the anterior commissure. Similar lesions are present in other fiber bundles. (*C*) Blood vessels are usually present within or adjacent to these focal lesions. (*D*) Multiple lesions in the stratum fibrosum of the tectum. A similar distribution of these lesions is seen throughout the brain stem and cerebellum. (*E*) Swollen and pale-staining glial cells and nerve cells in the focal lesions. The precipitated protein from the edema fluid provides a pale gray background for the photograph. Hematoxylin and eosin stain.

of these cells were swollen; their nuclei were vesiculated, and the chromatin material was compressed about the nucleolus. The tigroid substance was centrally depleted and compressed in large masses at the periphery of the perikaryon. Other cells were shrunken; their form was angular, and they stained deeply and homogeneously.

In the diencephalon, the cellular changes were the same as those described in the cerebral cortex. The fiber tracts, such as the forebrain bundles, the anterior and posterior commissures and the optic pathway, showed multiple focal areas of degeneration. These areas varied in size. They were irregularly circular, pale staining and confined to the myelinated fibers, as seen in hematoxylin and eosin preparations and in reactions stained for myelin sheaths. In these lesions a few nerve fibers were demyelinated and fragmented, while the majority were crowded to the periphery and compressed. Neuroglia cells, which were usually present, were swollen and pale staining, and the chromatin granules were thinly dispersed (fig. 1 *E*).

The changes in the brain stem were more pronounced than those in the forebrain. Many of the nerve cells here were shrunken and distorted, and their processes were corkscrew-like. The cytoplasm was devoid of Nissl material and stained a muddy purple with hematoxylin and eosin. The nuclei were shrunken, eccentric in position and homogeneously stained. Other nerve cells showed swelling and varying degrees of chromatolysis.

The brain stem was the site of numerous focal areas of degeneration, such as have been described in the diencephalon. These foci were abundant along the great fiber tracts. However, they were found throughout the reticular formation and in the laminations of the tectum. These lesions might be so great in number as to give a cribriform appearance to sections through these regions (fig. 1 *D*). Nerve cells were often involved in these areas of degeneration, and when seen they were swollen, pale staining and disintegrated (fig. 1 *E*). Dilated and necrotic blood vessels were frequently noted within or adjacent to these focal lesions (fig. 1 *C*). Osmic acid preparations revealed further that the nerve fibers were swollen and that the myelin sheaths were fragmented and consisted of globular masses of fat (fig. 2 *A*). Bielschowsky silver preparations showed that some axis-cylinders were fragmented.

Many of the Purkinje cells in the cerebellum were pyknotic and deeply stained (fig. 3 *E*). Others were swollen, and the chromatin material of the nuclei was centrally compressed and separated from the nuclear membrane by a cloudy, fluid zone. The Nissl substance in these cells was condensed into large flakes and displaced to the periphery of the cell body. In many cells no evidence of nuclear chromatin or tigroid material could be seen. Throughout the cerebellum the Purkinje cells were depleted. The cells of the cerebellar nuclei showed changes comparable to those seen in the brain stem. The granule cells, the Golgi cells and the basket cells were affected only in the moribund bird. The substantia alba cerebelli contained many

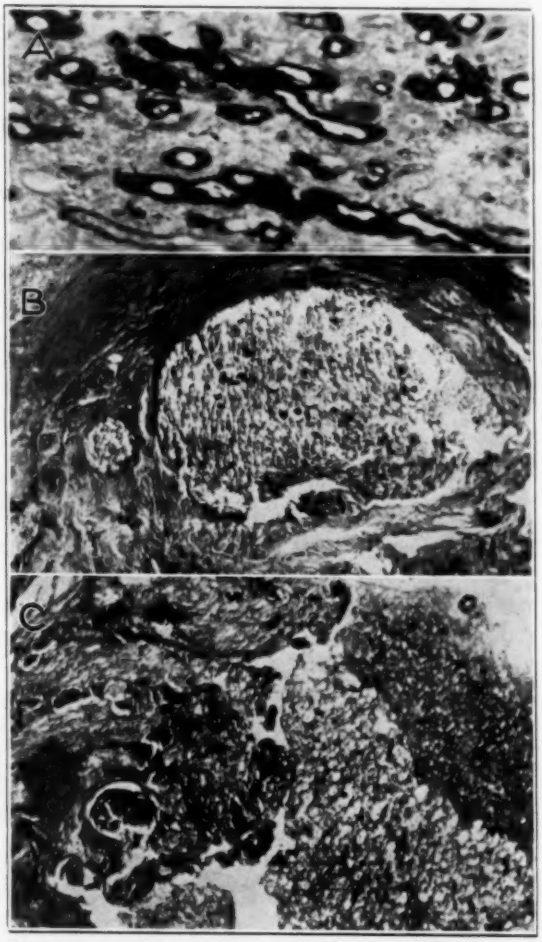

Fig. 2.—Extensive damage of the cranial and spinal ganglia and nerve roots. (*A*) Osmic acid preparation, showing that many myelinated fibers are swollen and fragmented. (*B*) Dorsal nerve root, showing extensive demyelination and fragmentation of the nerve fibers (hematoxylin and eosin stain). (*C*) Section of the trigeminal ganglion, showing destruction and depletion of the ganglion cells with fibrosis (hematoxylin and eosin stain). Round cell infiltration is present, but not visible in the photograph. The adjacent nerve root shows extensive demyelination.

focal areas of demyelination, similar to those already described (fig. 1).

The changes in the spinal cord were less conspicuous. The nerve cells, especially in the ventral horns, showed chromatolysis and altered staining reactions. Many cells were swollen.

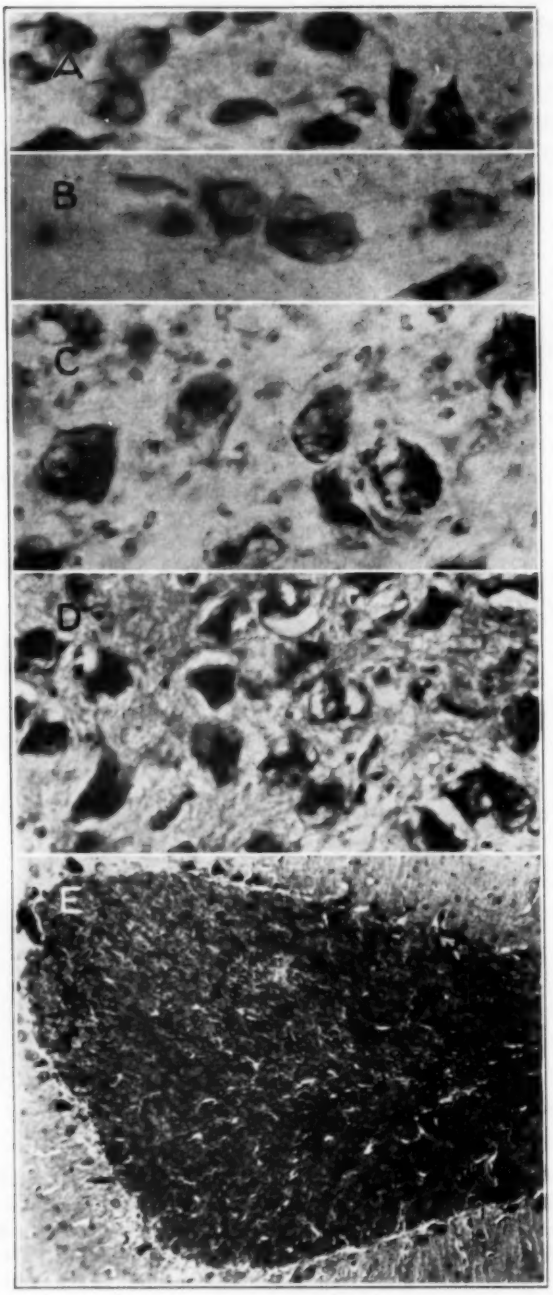

Fig. 3.—Extensive injury of nerve cells throughout the brain stem and cerebellum. (*A, B, C* and *D*) Swelling, vacuolation and fragmentation of nerve cells in various nuclei. (*E*) Folium of the cerebellum, showing pyknosis, edema, fragmentation and depletion of the Purkinje cells. This is a uniform change in all parts of the cerebellum. Hematoxylin and eosin stain.

The myelin sheaths and axis-cylinders in the long ascending and descending fiber pathways were swollen. The ventral funiculus and the spinocerebellar tracts were more involved than other regions of the cord. Rarely, a focal area of necrosis was seen in the spinal cord.

Many of the cells in the cranial, spinal and sympathetic ganglia exhibited swelling and chromatolysis, and the axis-cylinders and myelin sheaths of the corresponding nerve roots were swollen.

The brain and the spinal cord showed relatively few pathologic changes in the ducks that recovered from the acute malarial infection and did not present neurologic symptoms. The edema, which was a conspicuous feature in the ducks during the acute illness, was no longer present. The nerve cells throughout all portions of the nervous system in the ducks which did not show neurologic symptoms exhibited only minor alterations in structure and staining reactions, changes which were comparable to those seen in the normal controls except in the cerebellum, where the Purkinje cells were reduced in number.

The focal areas of degeneration, so conspicuous in the brain in the acute process, were greatly reduced in size and were filled in with glial tissue. They now appeared as irregular, pale-staining areas, in which the fibrous and glial matrix was less dense than the surrounding tissue.

In the ducks in which clinical neurologic disturbances developed the brains and cords showed in an exaggerated form all the characteristic lesions seen in the acute infections. Edema was a marked feature. The nerve cells, especially in the brain stem and the cerebellum, showed advanced degenerative changes. The cytoplasm, devoid of Nissl material, stained a muddy pink with hematoxylin and eosin, and the cells had a pale, shaggy appearance when stained with thionine. Many cells showed vacuolar degeneration and fragmentation of the nucleus and perikaryon (fig. 3). The nuclear masses functionally associated with the tectospinal, bulbospinal and spinocerebellar tracts and with the median longitudinal fasciculus were more extensively involved than the remaining nerve cells. The Purkinje cells and the cells of the cerebellar nuclei showed advanced degenerative changes.

The focal areas of degeneration in the birds with neurologic manifestation were larger and more numerous than they were in the birds with acute malarial infection. The ascending and descending pathways connecting the brain stem and cerebellum to the spinal cord showed pronounced swelling of the nerve fibers, with considerable fragmentation of the myelin sheaths. The motor pathways were more involved than the sensory tracts. These degenerative changes

were conspicuous in the median longitudinal fasciculus and the tectospinal, bulbospinal and spinocerebellar tracts.

The focal areas of degeneration, which were so conspicuous in the ducks showing neurologic symptoms, now appeared in these ducks which

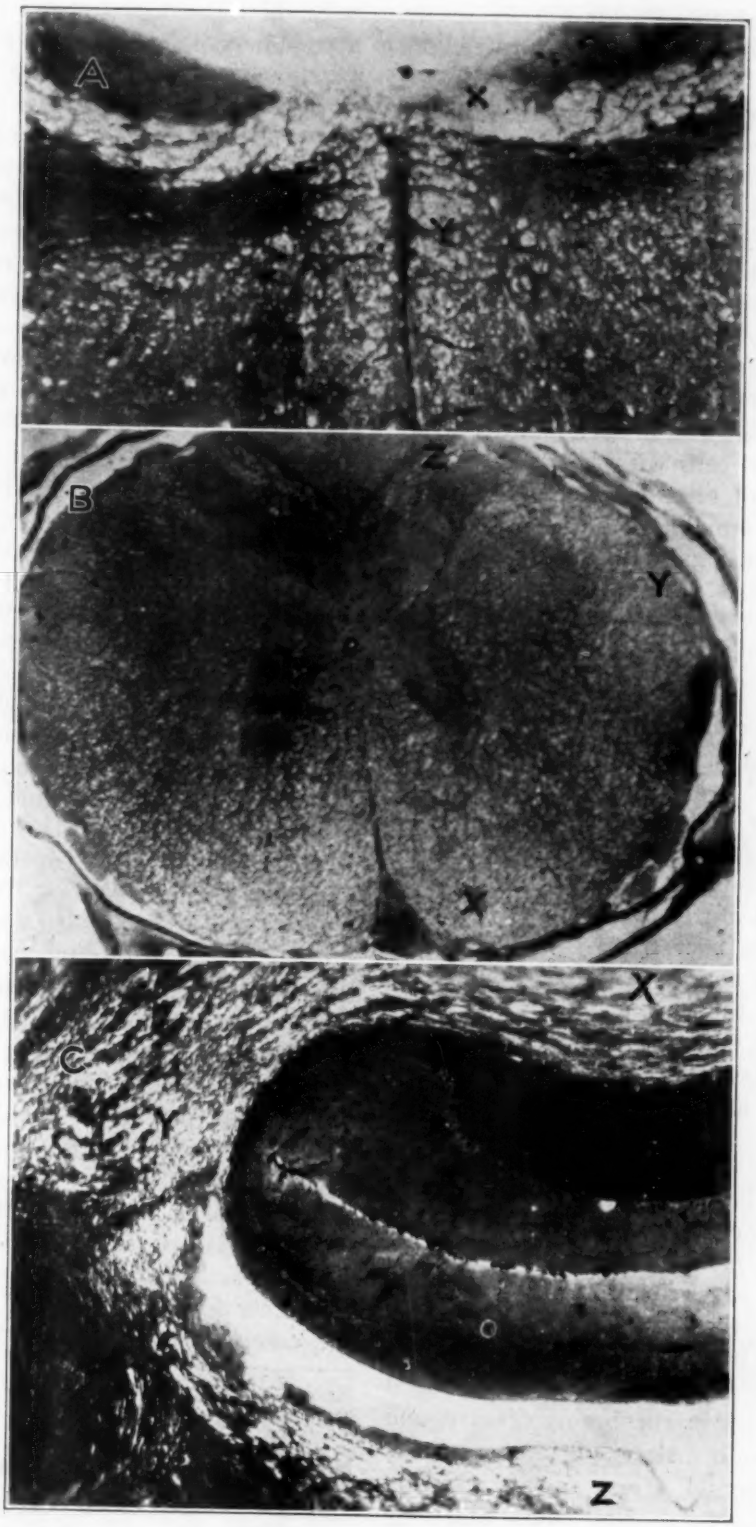

Fig. 4.—Extensive demyelination of the fiber tracts functionally associated with the cerebellum in ducks which have recovered from the neurologic manifestations. (*A*) Section through the medulla, showing extensive demyelination of the median longitudinal fasciculus (*X*) and the tectospinal tract (*Y*). (*B*) Section of the spinal cord, showing demyelination of the ventral funiculus (*X*), the dorsal and ventral spinocerebellar tracts (*Y*) and the dorsal fasciculus proprius (*Z*). (*C*) Section showing demyelination of the cerebellar commissure (*X*), cerebellar peduncle (*Y*) and median longitudinal fasciculus (*Z*). Hematoxylin and eosin stain.

had completely recovered from their neurologic disturbances as small, barely visible, pale-staining areas. No significant changes were observed in the nerve cells except that there was a notable depletion of the Purkinje cells in the cerebellum and an occasional fragmented cell in various nuclei of the brain stem.

In the medulla, the median longitudinal fasciculus, the tectospinal and spinocerebellar tracts (fig. 4 *A*) and the cerebellar peduncles and cerebellar commissure (fig. 4 *C*) had undergone extensive demyelination. The spinal cord also showed marked demyelination of the ventral funiculus and moderate involvement of the lateral funiculus, especially the dorsal and ventral spinocerebellar tracts, and the fasciculus proprius of the dorsal funiculus (fig. 4 *B*).

The trigeminal ganglion showed marked depletion of the ganglion cells with extensive fibrosis and infiltration with round cells and fibroblasts (fig. 2 *C*). The remaining ganglion cells appeared homogeneous and deeply stained. The emerging nerve roots were distorted, and their fibers were swollen and fragmented (fig. 2 *B* and *C*).

COMMENT

The clinical manifestations as observed in ducks with malaria may result from the pathologic changes noted in the nervous system. The lesions which occur in the nervous system during the acute phase of the infection are edema of the tissue, alterations in the staining reactions and morphologic features of the nerve cells and degeneration in the fiber tracts. The last-mentioned change may appear either as swelling and fragmentation of the myelinated nerve fibers or as focal lesions closely associated with blood vessels. The appearance of the focal lesions suggest that they are pockets of fluid. In this respect they are similar to the perivascular necrosis frequently observed in the human brain and considered to be the result of edema. However, these lesions are more numerous in the duck and, because the pressure of the accumulated fluid displaces the nerve fibers and glial elements to the periphery of the area, are more impressive than those seen in man.

The changes in the nerve cells are identical with those observed in the brains of man and monkey infected with malaria,[7] in dogs and cats following experimental arrest of the cerebral circulation[9] and in the human brain following ischemia.[10]

Pyknosis and hyperchromia are the first changes observed in the nerve cells during the course of the infection. These are followed, in turn, by chromatolysis, edema of the cell, vacuolation of the cytoplasm and cellular disintegration. The rapidity, severity and duration of the infectious process apparently determine the degree of cellular changes seen in any given case. There are differences of opinion among investigators as to the sequence and significance of these various cellular changes. The observation made in this study supports the interpretation of Gildea and Cobb[9b] that pyknosis represents the acute reaction of nerve cells to ischemia, while the edematous stage represents the more chronic reaction. The early responses result from stimulation of the cell and are normal physiologic changes. The later responses result from irreparable damage to the cell and are pathologic changes. Just where the line separating the normal from the abnormal is to be drawn in this series of events is a matter of opinion.

The earlier changes in both the nerve cells and the fiber tracts apparently are reversible, since they disappear with recovery from the malarial infection. It is suggested that as the degree of the parasitemia decreases and the red blood cell count rises, the normal osmotic relations are gradually restored, in consequence of which the edema recedes. As the fluid is withdrawn from the tissues, the nerve fibers and glial elements, released from pressure, again fill in and largely obliterate the focal lesions. The nerve cells also respond favorably to the improved osmotic conditions. Recovery from the clinical symptoms accompany these morphologic changes.

Many of the ducks which recover from the acute infection later manifest pronounced neurologic disturbances. These are accompanied with conspicuous pathologic changes in the nervous system. Similar observations have been made by other investigators, in various studies, but the mechanism for these delayed clinical manifestations is not known. Kabat,[11] Dennis and Kabat,[12] and Kabat, Dennis and Baker,[9a] by use of the cervical pressure cuff, completely arrested the cerebral circulation in dogs for periods of

9. (*a*) Kabat, H.; Dennis, C., and Baker, A. B.: Recovery of Function Following the Arrest of the Brain Circulation, Am. J. Physiol. **132**:737-747, 1941. (*b*) Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876-901 (May) 1930.

10. Courville, C. B.: Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif., Pacific Press Pub. Assn., 1939.

11. Kabat, H.: The Greater Resistance of Very Young Animals to Arrest of the Brain Circulation, Am. J. Physiol. **130**:588-599, 1940.

12. Dennis, C., and Kabat, H.: Behavior of Dogs After Complete Temporary Arrest of the Cephalic Circulation, Proc. Soc. Exper. Biol. & Med. **40**:559-561, 1939.

two to twelve minutes. Several of the dogs remained in coma for twenty-four to thirty-six hours, after which they manifested ataxia, tremor and loss of spontaneous activity. Courville,[10] while studying the effects of nitrous oxide anesthesia on the nervous system of man, observed that frequently an interval of several hours, days or weeks elapsed between the administration of the anesthetic and the appearance of the neurologic manifestations.

The lesions which are found in the ducks with neurologic manifestations, although more extensive, are identical with those present during the acute infection. If the opinion is correct that the pathologic changes occurring during the acute infection result from the altered cellular metabolism and from the accumulation of edema fluid incident to vascular disturbance, it is reasonable to believe that the subsequent lesions have a similar etiologic basis. The pertinent question is what factor produces these delayed vascular disturbances. The birds at the time of death did not appear to be anemic, and parasites were not demonstrated either in the peripheral blood or in stained sections of the brain. Therefore one cannot attribute the secondary vascular disturbances to an exacerbation of the infectious process.

It is of interest to know that Courville [10] observed remissions and exacerbations of symptoms with progressive neural deterioration in patients who had suffered cardiorespiratory failure under nitrous oxide oxygen anesthesia. It was his expressed opinion that these delayed clinical and pathologic manifestations result from vasomotor instability. He stated (page 69) [10] :

> . . . anoxemia so impairs the vasomotor control of the cerebral blood vessels that abnormal fluctuations in the vascular bed result, and these fluctuations are manifested clinically by remission or exacerbation in the patient's symptoms. This perverted action of the vasomotor system probably continues or even accentuates the destructive process. It is still another bit of evidence that asphyxia simply initiates the degenerative process, and the end results become evident only after a sufficient interval of time has elapsed.

Regardless of whether or not vasomotor instability is an adequate explanation, the fact remains that this subsequent disturbance is accompanied with a considerable degree of edema, extensive demyelination of the fiber tracts, necrosis of nerve cells and clinically manifest neurologic signs. These pathologic changes in the brain and spinal cord apparently are irreversible. They involve primarily the nuclei and sensory and motor tracts associated with the cerebellum and its functions.

The clinical manifestations shown by the ducks are definitely those resulting from cerebellar dysfunction. Muscular weakness, loss of coordination and ataxia are typical manifestations of cerebellar deficiency. The to and fro rocking motion and the inability alternately to flex and extend the leg and foot are analogous to the Romberg sign and adiadokokinesis observed in man. Furthermore, the symptoms are exaggerated when the ducks are blindfolded, which is also the case in man with lesions in the cerebellum. It is of interest that the neurologic manifestations exhibited by the experimental animals of Kabat and his associates [9a] were cerebellar in nature and that in many cases reported in the literature in which neurologic disturbances followed malaria in man cerebellar, in addition to cerebral, symptoms were shown.

Although these advanced pathologic changes in the nervous system are irreversible and persist, the affected ducks after several weeks make a satisfactory clinical recovery. Kabat's dogs, likewise, recovered from their neurologic disturbances. It is well recognized that birds, as well as many lower mammals, readily recover from the symptoms produced by partial or complete destruction of the cerebellum. In case of extensive damage to the human cerebrum and cerebellum, full clinical recovery should not be expected.

The spinal and cranial ganglia and their associated nerve roots were injured in most of the ducks infected with malaria. In some birds the damage was extensive. This is interesting in view of the clinical observations that patients with malaria commonly complain of neuritis (Harvey [1]). Bargeton [13] found that complete suppression of the blood supply to a sympathetic ganglion resulted in complete loss of activity, which was readily restored on removing the arterial obstruction. Repeated experiments on the same ganglion, however, led to rapid exhaustion, to slowed reaction and to delayed recovery of the cells.

Cannon and Burket [14] observed morphologic changes in the ganglion cells of the mesenteric plexus within three hours after occlusion of the blood supply. After three and a half hours practically all cells either had disappeared or were disintegrating. We have frequently observed in both ducks and chicks infected with malaria a depletion and fragmentation of cells

13. Bargeton, D.: Some Effects of Acute Anemia on the Transmission of Impulses Through a Sympathetic Ganglia, Am. J. Physiol. **121**:261-269, 1938.

14. Cannon, W. B., and Burket, I. R.: The Endurance of Anemia by Nerve Cells in the Myenteric Plexus, Am. J. Physiol. **32**:347-357, 1913.

in the celiac and aortic chain of ganglia. In view of the changes in the various ganglia and nerve roots, it is reasonable to assume that sensory disturbances were present in the ducks, although they were not evaluated in this study.

In a previous paper discussing the lesions in the brain associated with malaria,[7] we presented the concept that the pathologic changes result from anoxia. We believe, also, that anoxia is the primary etiologic factor responsible for the pathologic changes in the nervous system of ducks. This opinion is supported by the fact that we have experimentally produced identical lesions in ducks and chicks placed in the low pressure chamber.

Clinical and experimental observations show that pronounced anemia results from the rapid destruction of red blood cells by the malarial parasites. The oxygen-carrying capacity of the blood is thereby reduced. This anoxemic state not only affects the brain directly but produces a generalized circulatory "failing," which further increases the cerebral anoxemia and leads to cerebrovascular stasis and ischemia of the brain tissue. Increased capillary permeability results from damage to the capillary endothelium. Fluid escapes from the capillary walls into the perivascular spaces and the adjacent nerve tissue. Edema is thus produced. This results in stasis of the tissue fluids. Oxygen is thereby excluded from the tissue, and carbon dioxide accumulates in the pericellular and perivascular spaces. This leads to dilatation of the blood vessels and thus to further vascular stasis. The excessive accumulation of the edema fluid in the tissue spaces may produce the focal areas of degeneration which have been described. The depletion of oxygen to the nerves fibers and the pressure of the surrounding fluid lead to swelling, fragmentation and degeneration of the myelin sheaths. The nerve cells similarly affected undergo alterations in their size, shape and staining reactions. They become edematous and eventually fragment and disintegrate. The clinical manifestations are only the physiologic expressions of these morphologic alterations.

SUMMARY

Ducks severely infected with P. lophurae showed injury to the brain, spinal cord and peripheral ganglia and nerves. Pronounced edema; focal areas of degeneration in the fiber tracts; extensive demyelination of the nerve fibers, and pyknosis, edema and fragmentation of the nerve cells are the characteristic lesions. The nuclei and fiber tracts functionally associated with the cerebellum are the structures most extensively damaged. These pathologic changes are accompanied with clinical manifestations of cerebellar dysfunction, such as ataxia, incoordination and disturbances of posture and equilibrium. It is suggested that anoxia, which results, first, from the anemia produced by the rapid destruction of red blood cells by the parasites and, second, from vasomotor instability and circulatory failure, is the eiologic factor responsible for these pathologic changes.

University of Arkansas School of Medicine.

NYSTAGMUS

AN APPRAISAL AND A CLASSIFICATION

RUSSELL N. DeJONG, M.D.
ANN ARBOR, MICH.

Nystagmus is a common sign in diseases of the nervous system, and it is also observed in diseases of the eye and of the inner ear. It may, however, be a normal phenomenon in certain circumstances, or it may be elicited experimentally or as part of the clinical examination. There are many varieties of nystagmus, and the manifestation should not be considered as an entity. In order to evaluate the significance of the presence of nystagmus in any individual instance, one must understand the underlying mechanisms and the mode of production of the phenomenon.

Nystagmus, or, as it is sometimes called, talantropia,[1] may be defined as an involuntary oscillation or trembling of the eyeball. The term "rhythmic" is often included in the definition, but nonrhythmic varieties may be seen. Certain observers object to the inclusion of the adjective "involuntary," as nystagmus of volitional origin has been described. Nystagmus is a coordinated movement, and usually the two eyes move synchronously over a virtually equal range. Unilateral nystagmus, however, may occur, or there may be dissociation of movements or disproportion between the movements on the two sides. The motor response involves not only the contraction of certain muscles but the relaxation of their antagonists by reciprocal innervation, with alternating activity of agonists and antagonists.[2]

Nystagmus may be described in various ways, namely, as to type, form, direction, rate, amplitude, duration and intensity, and as to the relation of the response to movements of the eyes, head and body. It may be rhythmic or pendular in type. In rhythmic, or resilient, nystagmus, also known as jerky, biphasic, directed or spring nystagmus, there are alternate slow and quick ocular excursions, resulting in jerky, unequal oscillations of the eyeballs. Usually there is a rapid movement in the direction of gaze, which is followed by a slower return movement away from the point of fixation. In pendular, or undulatory, nystagmus there are more or less regular to and fro movements of approximately equal range and velocity toward each side of a central point.

Nystagmus may be horizontal, vertical, oblique, rotatory or mixed in form and may be directed to the right or left, or upward or downward. In rotatory nystagmus the direction is recorded as clockwise or counterclockwise to the right or to the left. Nystagmus may be slow, medium or rapid in rate, or velocity, and may vary from 10 to 1,000 oscillations per minute.[3] It is said that if the movements are from 10 to 40 per minute the nystagmus is slow; it is medium in velocity if the oscillations are between 40 and 100 per minute, and it is rapid if they are over 100 per minute. Nystagmus is classified as to amplitude, being fine, medium or coarse. The movements may be so gross that they cannot be overlooked, or they may be so fine that they cannot be seen with the naked eye but are visualized only when the eye is examined with the ophthalmoscope or when a + 20.00 D. lens is placed in front of the eye. The use of the convex lens not only magnifies the nystagmus but eliminates fixation. It is said that if the excursions are of less than 5 degrees or less than 1 mm. in amplitude the nystagmus is fine, if they are over 15 degrees or more than 3 mm. in amplitude the nystagmus is coarse and if they are between these values the nystagmus is considered of medium amplitude.[3] From the standpoint of duration nystagmus may be abortive or sustained. It may also be classified as to intensity; it is said to be of first degree intensity if present only when the subject is looking in the direction of the quick component, of second degree intensity if present not only when he is looking in the direction of the quick component but when the eyes are in the neutral position, and of third degree intensity

From the Department of Neurology of the University of Michigan Medical School and University Hospital.

1. Peter, L. C.: The Extra-Ocular Muscles: A Clinical Study of Normal and Abnormal Ocular Motility, ed. 3, Philadelphia, Lea & Febiger, 1941, p. 293.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1939, vol. 1, p. 630.

3. Spiegel, E. A., and Sommer, I.: Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc., 1944, p. 104.

if present even when he is looking in the direction of the slow component.

Nystagmus may be congenital or acquired; it may be spontaneous or artificial (or induced); it may be present at rest, on fixation or on deviation of the eyeballs. Nystagmus may be associated or conjugate, with the movements symmetric in the two eyes, or dissociated, with the movements of the two eyes unrelated. In unilateral nystagmus the movements are seen on one side only. In disjunctive nystagmus, which is rare, the movements are symmetrically opposite. A movement that appears to be simple to the naked eye may be seen to be irregular or complex when visualized through the ophthalmoscope or through a lens. Nystagmus may vary from time to time in the same person, depending on such factors as the position of the body, the head and the eyes. Nystagmus may be maintained or unimpaired in the presence of extensive ocular palsies.[2] Rhythmic movements of the head may accompany nystagmus. Patients with nystagmus may notice a sensation of movement at the onset of the manifestation, or they may notice a constant movement of the objects within the field of vision; this subjective manifestation is known as oscillopsia and is relatively rare.[4]

Various methods have been described for the delineation and recording of nystagmus. Among the modes first utilized were mechanical means such as that of Ohm,[5] who placed tambours against the closed eyelid, using a pneumatic tube to transmit the movements of the eyeball to a kymograph. With later methods the electrical potentials set up by ocular movements were recorded, either an oscillograph with an amplified pick-up, basically a modified string galvanometer,[6] or a vacuum tube amplifier[7] being used to show resistance capacity. All these methods have certain drawbacks, however. The pressure of the tambour and the lag in conduction of the impulse may inhibit or diminish the recording of the amplitude and duration of the movement. With the electrical methods, the electrodes are attached to the outer canthi or to the temples, and one gets a recording not only of the movements of the eyeball but of the movements of the eyelid, the orbicularis muscle and the head. In experimental work the electrodes can be attached to the anesthetized cornea or to the ocular muscles, but these methods are not applicable to clinical study.

Photographic methods have been used by Dodge and Fox,[8] Linthicum[9] and others. The first-named authors pressed a concave mirror against the closed lid of one eye tangential to the underlying corneal surface, and this reflected a recording beam of light on moving photographic paper, thus showing the conjugate movement of one eye as the other moved in response to visual or other stimuli. With this method, also, movement of the levator and orbicularis muscles, tremors, movements of the head and fatigue influence the recording. Linthicum focused a beam of light against the eye, and the corneal light reflex was focused on a continuous photographic film. Cinematography has also been used, but it is difficult to record the amplitude and rate with this method. At present there is no clinically applicable method with which nystagmus is adequately recorded so as definitely to delineate rate, amplitude, type, duration and intensity. The character and extent of the oscillations may be most satisfactorily studied by means of the slit lamp, utilizing the f/55 objective with a micrometer ocular; this enables the observer to study the character of the movement and to measure the amplitude of the oscillations. The Ferree-Rand perimeter can also be used for similar observations.[10]

Nystagmus must not be regarded as an entity, for there are many types of nystagmus which appear to serve widely diverse purposes. The position of the eyes is influenced reflexly by

4. Brickner, R. M.: Oscillopsia: A New Symptom Commonly Occurring in Multiple Sclerosis, Arch. Neurol. & Psychiat. **36**:586 (Sept.) 1936.

5. Ohm, J.: Ein neuer Nystagmograph, Klin. Wchnschr. **4**:1286 (June 25) 1925; Die Hebelnystagmographie: Ihre Geschichte, Fehler, Leistungen und Vervollkommung, Arch. f. Ophth. **120**:235, 1928.

6. Meyers, I. L.: Electronystagmography: A Graphic Study of Action Currents in Nystagmus, Arch. Neurol. & Psychiat. **21**:901 (April) 1929. Fenn, W. O., and Hursh, J. B.: Movements of the Eyes When the Lids Are Closed, Am. J. Physiol. **118**:8 (Jan.) 1937. Smith, K. U.; Kappauf, W. E., and Bojar, S.: The Function of the Visual Cortex in Optic Nystagmus at Different Velocities of Movement in the Visual Field, J. Gen. Psychol. **22**:341 (April) 1940.

7. Perlman, H. B., and Case, T. J.: Nystagmus: Some Observations Based on Electrical Method for Recording Eye Movements, Laryngoscope **49**:217 (March) 1939.

8. Dodge, R.: A Mirror-Recorder for Photographing the Compensatory Movements of Closed Eyes, J. Exper. Psychol. **4**:165 (June) 1921. Dodge, R., and Fox, J. C., Jr.: Optic Nystagmus: I. Technical Introduction, with Observations in a Case with Central Scotoma in the Right Eye and External Rectus Palsy in the Left Eye, Arch. Neurol. & Psychiat. **20**:812 (Oct.) 1928. Fox, J. C., Jr., and Dodge, R.: Optic Nystagmus: II. Variations in Nystagmographic Records of Eye Movements, ibid. **22**:55 (July) 1929.

9. Linthicum, F. H.: Nystagmography: A Method for the Graphic Recording of Nystagmus During and After Turning and of Caloric Nystagmus, Arch. Otolaryng. **32**:464 (Sept.) 1940.

10. Peter,[1] p. 300.

impulses coming from the retinas, the ocular muscles, the labyrinths and the cochlea and by proprioceptive impulses arising from movements of the head or body. It is also influenced by impulses arising centrally from the motor cortex. Nystagmus may, in most instances, be considered a compensatory reaction of the eyeballs to defective or abnormal impulses arising from any of these sources. It may serve many apparent purposes: namely, to retain a specific field of vision,[11] i. e., to keep the eyes as long as possible in the same position in relation to the visual field; to increase incoming impulses; to aid in ocular fixation, and to assist in orientation in space.

If the head moves or if the field of vision moves, the eyes move in the opposite direction in an attempt to remain fixed in the original field, to maintain as long as possible the same position relative to the visual field or to preserve the image of the fixed object on the retina. Because of the limited excursion of the eyes, however, the original field cannot be held, and at their maximal deviation the eyes are jerked back to take up a new focus; this is a corrective movement and is too quick to allow for visual apperception. These conjugate movements of the eyes constitute the underlying mechanism for the production of nystagmus. If the labyrinth on one side is stimulated by repeated movements of the head or body or by some other means, there is a slow movement of the eyes toward one side, again in an attempt to retain the original field of vision. The eyes cannot, however, be held in this position, and they are jerked back to take up a new focus in relation to the environment. If these movements persist, nystagmus results. If, owing to poor macular vision, inadequate visual acuity or inadequate illumination, the impulses focused on the macula are not sufficient to allow adequate perception, the eyes move from side to side in an attempt to increase or reenforce the incoming visual impulses, to find the sharpest image or to achieve adequate fixation, with no relation to movement of the head or of the field of vision. Here, also, nystagmus results, but the movements are equal in amplitude and rate toward each side. If nystagmus results from the movement of the field of vision or from attempts to increase vision, it is a reflex response to retinal stimulation and may be called an oculocerebral reflex. If it results from movement of the head or body or from irritation of the labyrinth, it is a reflex response to vestibular stimulation and may be called a vestibulocerebral reflex. Other mechanisms in the production of nystagmus will be described in the discussion of the specific varieties. Owing to the integrative action of the various components of the nervous system and their correlation and interdependence, it is often impossible to separate entirely visual, sensory (proprioceptive), vestibular and other factors.

The slow movement in rhythmic nystagmus is the compensatory one and is of primary importance from the functional point of view. This component is said to be of peripheral or vestibular origin. Its purpose is to preserve the image of the fixed object on the retina. The reflex arc involves the labyrinths, the vestibular nuclei, the medial longitudinal fasciculus, the nuclei of the extraocular muscles and the ocular muscles themselves. The rapid phase is often referred to as the cerebral, or central, component. It has been observed to disappear during anesthesia and to return with the return of consciousness. Fox and Holmes[12] placed the reflex center of "optic nystagmus," and therefore the center regulating the rapid component of nystagmus, in the occipital lobe, with communications to the second frontal convolution. McIntyre[13] stated that the rhythm of nystagmus is entirely central in origin and is independent of impulses from the ocular muscles, and Meyers[14] observed that the quick component was abolished by lesions in that portion of the motor cortex which is concerned with ocular movements. Wilson and Pike[15] found that the quick component of labyrinthine nystagmus was abolished by experimental complete removal of the cerebrum in dogs and cats, provided such removal included the optic thalami. Ivy,[16] however, stated that the quick component is not dependent on the integrity of a cerebral reflex arc but, rather, has its center below the thalamus, on which the cerebrum has inhibitory influences. It is now known that nystagmus persists after extirpation of the hemispheres, and even after section of

11. McNally, W. J.: Nystagmus, Graduate Lecture, Course no. 326, American Academy of Ophthalmology and Otolaryngology.

12. Fox, J. C., and Holmes, G.: Optic Nystagmus and Its Value in the Localization of Cerebral Lesions, Brain **49**:333 (Sept.) 1926.

13. McIntyre, A. K.: The Quick Component of Nystagmus, J. Physiol. **97**:8 (Nov. 14) 1939.

14. Meyers, I. L.: Nystagmus: Neuro-Otologic Studies Concerning Its Seat of Origin, Am. J. M. Sc. **169**:742 (May) 1925.

15. Wilson, J. G., and Pike, F. H.: The Mechanism of Labyrinthine Nystagmus and Its Modifications by Lesions in the Cerebellum and the Cerebrum, Arch. Int. Med. **15**:31 (Jan.) 1915.

16. Ivy, A. C.: Experimental Studies on the Brain Stem: II. Comparative Study of the Relation of the Cerebral Cortex to Vestibular Nystagmus, J. Comp. Neurol. **31**:1 (Oct.) 1919.

the brain stem to the level of the nucleus of the oculomotor nerve.[17] It has been shown that the only part of the central nervous system essential for the production of the slow and quick phases of nystagmus is that portion situated between the oculomotor nuclei, above, and the vestibular nuclei, below.[11] Spiegel placed the center for the quick component within the vestibular nuclei and regarded these nuclei as the site of origin of both the slow and the rapid component of nystagmus.[18] Lorento de Nó[19] expressed the opinion that there is a rhythmic center situated within the vestibular area, probably in the reticulate substance, the intactness of which is essential to the quick phase, but Spiegel and Sommer[18] asserted that such a center is not necessary and stated that both the slow and the quick phase have their origin in the vestibular nuclei and that the rhythm is dependent on reciprocal inhibition and a refractory phase.

Other parts of the nervous system may, however, exert a profound influence on the nystagmus. The center for the volitional control of conjugate ocular movements, situated in the caudal portion of the middle frontal gyrus (area $8\,\alpha\,\beta\,\delta$), sends fibers through the internal capsule and the cerebral peduncle, from whence they descend with the aberrant pyramidal fibers.[20] They probably reach the nuclei of the ocular nerves in the midbrain and pons through the medium of the medial longitudinal fasciculus.[21] The zone immediately surrounding the area striata, corresponding to fields 18 and 19 of Brodmann, is the cortical center for optically induced ocular movements and optic fixation reflexes. Corticofugal fibers from this center pass through the posterior limb of the internal capsule to the superior colliculus (anterior quadrigeminal body) and thence through the medial longitudinal fasciculus to the nuclei of the ocular nerves. Through the latter pathway the optomotor fibers also have connections with the vestibular nuclei, the accessory nuclei and nuclear centers in the upper cervical portion of the cord. There are also association pathways from the occipital to the frontal cortical areas, with radiation of optomotor impulses to the frontal cortex, before they descend to the brain stem. It may be that the pathways from the cortex that have to do with conjugate ocular movement pass through the vestibular nuclei before they synapse with the nuclei of the ocular nerves. Through the aforedescribed mechanisms, impulses for volitional and reflex controls not only bring about conjugate ocular movements but are of importance in the production or inhibition of nystagmus.[22]

Nystagmus has long been known, but its significance has not been adequately appreciated and its manifestations have not been classified. Even the nomenclature is etymologically incorrect, since the word "nystagmus," as directly translated from the Greek word νυσταγμος, means "drowsiness." This noun is derived from the verb νυσταξω, which means "to doze," "to be half-asleep," implying, perhaps, "to nod off to sleep."[23] The notion of nodding or jerking could be present in the derivative noun but is absent in the direct translation. Authors and textbooks differ in classification and interpretation. The terminology is often confusing. Clinicians, in referring to rhythmic nystagmus, usually name it from the direction of the rapid component, as this movement is more readily noticed and is more striking. The slow phase, however, represents the more active physiologic determinant and is therefore the primary movement, and in writings of experimental workers, anatomists and physiologists, the nystagmus is named after this phase. It would be better if the latter terminology were accepted by all or if the direction were qualified when noted.

There is a lack of integration of scattered facts regarding the phenomenon, both as it appears in normal persons in response to certain types of stimulation and as it is observed clinically as an expression of disease of the central nervous system, the eyes or of the ear.[23] Nystagmus is spoken of as being physiologic or pathologic, but these terms are only relative in significance, and the so-called physiologic varieties may be evidenced in the presence of diseases of the nervous system, whereas the so-called pathologic varieties do not always imply the presence of a significant disease process. Nystagmus is also often classified as being of ocular, vestibular or neurologic (or central) origin, but these terms are generalities and do not adequately explain the underlying processes. Nystagmus may be induced clinically or experimentally by certain tests or methods of stimulation. This is called induced, or experimental, nystagmus and is usually a physiologic phenomenon. Other varie-

17. Duke-Elder,[2] p. 631.

18. Spiegel and Sommer,[3] p. 77.

19. Lorente de Nó, R.: The Regulation of Eye Positions and Movements Induced by the Labyrinth, Laryngoscope **42**:233 (April) 1932.

20. German, W. J., and Fox, J. C., Jr.: Observations Following Unilateral Lobectomies, A. Research Nerv. & Ment. Dis., Proc. **13**:378, 1932.

21. Walsh, F. B.: Certain Abnormalities of Ocular Movements: Their Importance in General and Neurologic Diagnosis, Bull. New York Acad. Med. **19**:253 (April) 1943.

22. Spiegel and Sommer,[3] p. 411.

23. Fox, J. C., Jr.: Nystagmus, Yale J. Biol. & Med. **1**:224 (March) 1929.

ties are caused by disease or irritation of any of the structures concerned with vision, ocular movement or equilibrium. Such nystagmus is spontaneous and is of clinical significance. There may, however, be mixed forms and irregular types of each. Any classification of nystagmus is subject to criticism, as it must be somewhat arbitrary and subject to exceptions; but classification is justifiable if it aids in the interpretation of the phenomenon and adds to one's knowledge of the significance of the manifestation. The following classification is presented for the sake of clarity, as it seems to correlate fairly effectively the many varieties. It is realized, however, that there are discrepancies in the terms, and they must be considered as relative, and not exclusive. Furthermore, the classification must not be considered as an etiologic one, and it is presented principally as a basis for further study. Later knowledge regarding the mechanism of the phenomenon, the site of origin of the component parts, and other factors, may radically alter it.

INDUCED NYSTAGMUS

This type of nystagmus is produced clinically or experimentally by certain tests or methods of stimulation. The resulting varieties are usually considered physiologic, and they may be induced in normal persons. Changes in the responses, however, occur with disease processes.

1. *Opticokinetic Nystagmus.*—This variety of nystagmus has been known by a variety of names. Fox and Holmes [12] and many others have referred to it as optic nystagmus; others have used the terms optokinetic, optomotor or opticomotor. It is elicited when a drum or an umbrella painted with vertical stripes is rotated rapidly in front of the eyes or when a person in a rapidly moving vehicle directs his eyes toward fixed objects. It is sometimes called railway, or elevator, nystagmus. It is a conjugate or conjunctive response of the eyes to a succession of moving visual stimuli. The nystagmus is fine, rapid and rhythmic, and it is usually horizontal in direction, depending on the direction of the movement of the body or of the moving object; if the drum is held and moved horizontally, the nystagmus is vertical. When a rotating drum is used, the slow phase is in the direction of the movement of the drum, and the quick phase is in the opposite direction. When the subject is in a train, the slow phase is in the direction of the moving field of vision,[12] and the quick phase is in the direction in which the subject is moving. Thus, the slow phase seems to indicate the pursuit of the moving object,[24] with a quick return in an attempt at fixation on a new, oncoming object. The response is intensified if the subject looks in the direction of the quick phase. When the subject attempts to fix the eyes on a series of objects moving past in rapid succession, the object is followed until its successor is in the field of consciousness. As the image of each successive object falls on the periphery of the retina, the eye is at once moved reflexly with a jerk in an attempt to bring the new object into the macular field. This phenomenon is a reflex response to retinal stimulation or to proprioceptive impulses from the muscles of the eye and has been believed to be cortical in origin, probably representing a cortical or an oculocerebral reflex.

Opticokinetic nystagmus is a physiologic response, and its absence must be regarded as pathologic. Fox and Holmes [12] found it to be lost to the opposite side with lesions of the temporal and parietal lobes, between the visual cortex and the second frontal convolution. It has also been found to be absent in cases of homonymous hemianopsia, especially when visual objects are moving from the blind to the normal field.[23] This loss may be temporary.[20] Fox made the observation that lesions in the posterior portion of the hemisphere, particularly in the region of the supramarginal or the angular gyrus or in the adjacent part of the parietal, occipital or temporal lobe, affected opticokinetic nystagmus when the visual objects were moving in a direction toward the side of the lesion.[25] In 2 of 5 cases of tumor of the frontal lobe there was also a change in the nystagmus, but the phenomenon was not modified by lesions in the superior portion of the cerebral hemisphere. Fox expressed the belief that this change in the nystagmus could not be explained solely on the basis of imperfect recognition and stated that an interruption of the corticofugal pathways at any point along their course disturbs the ocular response to movements toward the side of the lesion. He stated that the frontal lobe probably plays a secondary role in the mechanism underlying opticokinetic nystagmus. Smith [26] found that removal of the occipital lobes increases the time necessary for inactivation or extinction of opticokinetic nystagmus. He expressed the belief that the frontal cortex exerts an inhibiting mechan-

24. Dodge, R.; Travis, R. C., and Fox, J. C., Jr.: Optic Nystagmus: III. Characteristics of the Slow Phase, Arch. Neurol. & Psychiat. **24**:21 (July) 1930.

25. Fox, J. C., Jr.: Disorders of Optic Nystagmus Due to Cerebral Tumors, Arch. Neurol. & Psychiat. **28**:1007 (Nov.) 1932.

26. Smith, K. U.: The Effect of Partial and Complete Decortication upon the Extinction of Optic Nystagmus, J. Gen. Psychol. **25**:3 (July) 1941.

ism, controlling the responses toward the opposite side. Spiegel referred to two types of opticokinetic nystagmus: a cortical variety, which is dependent on concentration, and a subcortical, or passive, variety, which is independent of attention and may be found after extirpation of the hemispheres.[27] The production of the latter type is dependent on the intactness of the superior colliculi.

Inasmuch as opticokinetic nystagmus is a normal response, the rotating drum test is sometimes used to demonstrate feigned or simulated blindness in a malingerer, to diagnose hysterical blindness and to test for the presence of vision in an infant.[28]

2. *Labyrintine Nystagmus.*—This type of nystagmus is a physiologic response which follows the stimulation of the semicircular canals by rapid rotation of the body, by spraying the external auditory canal with warm or cold water, by galvanic stimulation or by changes in pressure. It is believed that the stimulation sets up a current or lymphokinesis in the endolymph within the semicircular canals and that this, in turn, stimulates the vestibular nerves. It cannot be definitely stated, however, whether the endolymph is static in the resting subject and is in motion only on stimulation of the labyrinth, or whether the fluid is bidirectional in the resting subject and becomes unidirectional on stimulation. Some authorities express the belief that there is no circulation of the fluid but that a change in pressure of the labyrinthine fluid stimulates the crista ampullaris. It is generally accepted, however, that the movement of the endolymph completely and consistently explains and accounts for the phenomenon. The resulting nystagmus is rhythmic. Its direction depends on the semicircular canals stimulated, and is thus dependent on the position of the head during stimulation; the direction also varies with the type and intensity of stimulus used. It has been stated by some authorities, among these being Favill [29] that each canal apparently has a major control over that pair of ocular muscles which moves the eyes in the plane of the canal. Thus, the horizontal canals exert a major control over the internal and external rectus muscles; the anterior vertical canals, over the superior and inferior oblique muscles, and the posterior vertical canals, over the superior and inferior rectus muscles. It is probable, however, that each labyrinth, directly or indirectly, has connections with all the ocular muscles of each eye through the medium of the medial longitudinal fasciculus, without a special relationship between canals and muscles.[30]

The slow phase of the nystagmus is said to be the resultant effect of the stimuli caused by the movement of the endolymph in the semicircular canals of the labyrinth. The head and eyes, and sometimes the body, are deviated in the direction of the endolymph current, and the slow phase of the nystagmus corresponds. The rapid phase, after which the nystagmus is often named, is in the opposite direction. The excitation of a single semicircular canal produces nystagmus only in a plane parallel with the plane of that canal (Flourens' law), and the relation between the direction of the flow of the endolymph and the direction of the nystagmus is a definite and constant one. Reversal of the flow of the endolymph causes a reversal of the direction of the nystagmus. Stimulation of more than one canal produces a more complex type of nystagmus. It is stated that a horizontal semicircular canal is maximally stimulated by a movement of the endolymph within the canal toward its ampulla, and a vertical canal is maximally stimulated by a movement of the endolymph away from the ampulla (Ewald's first law). Furthermore, maximal stimulation of a semicircular canal results in nystagmus with the rapid component toward the stimulated side, while minimal stimulation causes nystagmus with the rapid component toward the opposite side (Ewald's second law [11]).

(*a*) Rotational Nystagmus: This type of nystagmus is produced by use of the Bárány chair. The subject is rotated rapidly, about ten times in twenty seconds, and the rotation is then abruptly stopped. The head is held fixed by a head rest, and the eyes are closed to prevent the development of opticokinetic nystagmus. At the beginning of rotation, owing to inertia, the endolymph moves less rapidly than does

27. Scala, N. P., and Spiegel, E. A.: Subcortical (Passive) Optokinetic Nystagmus in Lesions of the Midbrain and of the Vestibular Nuclei, Confinia neurol. **3**:53, 1940.

28. Snell, A. C.: The Optokinetoscope, Tr. Am. Acad. Ophth. **44**:396, 1939.

29. Favill, J.: The Relationship of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus, Chicago, Privately Printed, 1936; An Explanation of the Mechanism of Induced Rotary and Vertical Nystagmus, Arch. Neurol. & Psychiat. **13**: 479 (April) 1925; The Twenty-Six Normally Possible Forms of Rotationally Induced Nystagmus, ibid. **19**: 318 (Feb.) 1928.

30. Bárány, R.: The Relationship Between Semicircular Canals and the Eye Muscles: The Central Mechanism in Vestibular Nystagmus, in Transactions of the Ninth Otological Congress, 1912, pp. 592-595. Quix, F. H.: The Function of the Vestibular Organ and the Clinical Examination of the Otolith Apparatus, J. Laryng. & Otol. **40**:425 (July); 493 (Aug.) 1925.

the body, and there is an apparent movement in the direction opposite the direction of the body. As a consequence, during rotation, the eyes are drawn to the opposite side, and the slow phase of the nystagmus is opposite the direction of rotation, with the recovery jerks, or the rapid phase, in the direction of rotation. When the rotation ceases abruptly, the momentum of the labyrinthine fluid causes it to continue to move in the direction of the recently completed movement of the body, even though the head is now stationary.[31] This causes the after-nystagmus, which is what one observes clinically, and it is opposite in direction to the primary nystagmus. The movements of the head, body and eyes, including the slow phase of the nystagmus, are in the direction of the recently completed rotation, whereas the rapid phase is in the opposite direction. In rotation tests, the nystagmus described is usually the after-nystagmus. Depending on a number of factors, including the rate and duration of the rotation and the sensitivity of the labyrinthine apparatus, the examiner may observe past pointing or kinetic deviation and postural deviation or falling, and the subject may also experience vertigo, nausea and vomiting, and sometimes even diaphoresis, prostration and shock. The direction of the nystagmus depends on the semicircular canal or canals that are stimulated. If the head is tilted forward 30 degrees, so that the horizontal canals are in the horizontal plane, horizontal nystagmus will result. If the head is tilted forward 90 degrees, backward 60 degrees or laterally 90 degrees, the vertical canals will be stimulated, and rotatory, or vertical, nystagmus will result. Diagonal and mixed nystagmus is produced by stimulating more than one set of canals.

(*b*) Thermal or Caloric Nystagmus: This form of nystagmus is produced by douching the external auditory canals with hot water (40 to 45 C., or 104 to 113 F.) or cold water (20 to 21 C., or 68 to 70 F.) or by introduction of hot or cold air. A more prompt response may be obtained with the use of ice water (0 to 10 C., or 32 to 50 F.). It is said that the change in the temperature of the endolymph causes it to circulate and that only those canals which are in the vertical plane are affected. Cold water causes the endolymph to flow from above downward and toward the side stimulated, whereas hot water has the opposite effect. Some authorities, however, doubt the production of a thermal current in the endolymph and state that the hot or cold water may stimulate the labyrinth directly or, through vasomotor changes, may cause an increase or a fall in labyrinthine pressure. Possibly the vestibular endings are stimulated directly if the water is too hot or too cold, and there may be an associated change in the tonus of the otolith organs secondary to the change in the temperature.[32] If the patient is examined in the prone position with the head tilted 30 degrees forward, or in the seated position with the head tilted forward 90 degrees or backward 60 degrees, the horizontal canals are vertical in direction and can be stimulated, with resulting horizontal nystagmus; if the subject is lying supine with the head tilted forward 90 degrees or backward 60 degrees, or is seated with the head tilted forward 30 degrees, the anterior vertical canals are stimulated, with resulting rotatory nystagmus. The posterior vertical canal is too far distant from the middle ear for stimulation in this test. With the use of cold water, the slow phase of the nystagmus, as well as the past pointing and postural deviation, will be toward the side stimulated, while the recovery jerks, or the rapid phase of the nystagmus, will be in the opposite direction. Hot water will produce the opposite effects.

(*c*) Nystagmus Induced by Galvanic Stimulation: The vestibular endings are probably stimulated directly and the movement of the endolymph in the semicircular canals is not ordinarily affected. When the anode is used as the stimulus, the slow phase will be toward the side stimulated, and with the cathode the opposite response is obtained. Inasmuch as a strong current is sometimes followed by an after-nystagmus, it is possible that the electrical stimulus may also cause movement of the endolymph.

(*d*) Compression Nystagmus: Unilateral changes in pressure in the semicircular canals by means of the experimental introduction of a pipet manometer into one of them or by alterations in the pressure of the middle ear by such factors as infection may produce nystagmus. An increase in pressure causes nystagmus with the slow phase to the opposite side, and a decrease in pressure results in nystagmus with the slow phase to the same side.[33]

Comment: Labyrinthine, or vestibular, nystagmus is a reflex response to movements of the head or body or to stimulation of the labyrinth and is thus a vestibulocerebral reflex. Pathologic variations of the response may accom-

31. Duke-Elder,[2] p. 633.

32. Mygind, S. H.: How Does Caloric Nystagmus Arise? J. Laryng. & Otol. **40**:444 (July) 1925.

33. Fischer, J., and Wolfson, L. E.: The Inner Ear, Including Otoneurology, Otosurgery, and Problems in Modern Warfare, New York, Grune & Stratton, Inc., 1943, p. 86.

pany disease processes, and modifications may be produced by experimental means. An unequal response on the two sides, a perversion of response or a dissociation of response with vertigo and past pointing but without nystagmus, all indicate lesions of the vestibular centers or their central connections. With lesions of the brain stem, one may find absence of response from one set of canals with preservation of the response from the other canals. It is stated that the reflex process is independent of all impulses or activities other than the afferent path from the labyrinth, the nuclei of the muscles concerned and a single efferent motor path. However, ocular inhibition in animals may change or decrease the labyrinthine nystagmus,[31] and it is entirely possible that proprioceptive impulses arising from the body or the cerebellum, other than those conveyed through the vestibular system, and possibly proprioceptive impulses from the ocular muscles, may alter the response. The part that the semicircular canals play in the reflex is not known, and rotational vestibular nystagmus may be produced with the semicircular canals tied off at the ampullae. The cerebral cortex also influences vestibular nystagmus, and voluntary movements of the eyes toward the side of the quick component accentuate the response. After the removal of one temporal lobe or cerebral hemisphere, experimental labyrinthine nystagmus with the slow component toward the side opposite the lesion is more easily elicited and of greater intensity than is that with the slow phase toward the involved side. It has been stated that the directional predominance (*Nystagmusbereitschaft*) is toward the extirpated side, but this refers to the quick component of the nystagmus.[34] The nystagmus may be diminished when the slow component is directed toward the side of the lesion.[35] The cerebrum does not enter into the reflex arc of labyrinthine nystagmus, but it does exert an inhibitory control over the reflex. The cerebellum may also have an inhibitory effect on labyrinthine nystagmus, and this inhibition is reduced with cerebellar lesions. Pigeons with cerebellar lesions do not become habituated to labyrinthine nystagmus as readily as do controls.[36] Acrobats, dancers, aviators and persons who are employed in work requiring rapid movements of the body in space have a reduced labyrinthine nystagmus. The nystagmus that results from vestibular stimulation may be diminished, and even extinction can be produced, by repeated rotations of the body. This is probably not the result of pathologic changes in the nervous system that are produced by the repeated rotations, and the diminished nystagmus does not interfere with equilibration but may even aid it. That dancers, for example, who have diminished nystagmus, and animals in which the nystagmus has been reduced by repeated rotations of the body have what appears to be better equilibrium than normal may be due to the fact that postural and kinetic deviation and the somatic and visceral effects of rotation, such as nausea, are also reduced, and these manifestations are incompatible with muscular coordination and equilibrium.[37]

3. *Reflex Acoustic Nystagmus.*—Rhythmic nystagmus results from loud auditory stimuli. The quick component is toward the side of the stimulus.

4. *Reflex Sensory Nystagmus.* — Rhythmic nystagmus follows stimulation of the skin in the neighborhood of the ear on pressure on the tragus. Here, also, the quick component is toward the side of stimulation. Handling of the eyelids during examination may also produce a reflex sensory nystagmus.

5. *Chemical or Toxic Nystagmus.*—Nystagmus is known to result from the use of drugs and from association with various toxins (see page 55). Chemical stimulation can also be used to produce experimental or induced nystagmus. Pentobarbital injected intravenously in rabbits produces a nystagmus of long duration, which appears at the initiation and at the cessation of narcosis.[38]

PATHOLOGIC VARIETIES OF NYSTAGMUS

These forms of nystagmus, in most instances, indicate the presence of an abnormal process in the eyes, the ocular muscles or the central connections concerned with ocular movement or

34. De Kleyn, A.: Some Remarks on Vestibular Nystagmus, Confinia neurol. **2**:257, 1939. Fitzgerald, G., and Hallpike, C. S.: Studies in Human Vestibular Function: I. Observations on the Directional Preponderance ("Nystagmusbereitschaft") of Caloric Nystagmus Resulting from Cerebral Lesions, Brain **65**:115 (June) 1942.

35. Wilson and Pike.[15] Ivy.[16]

36. Halstead, W.; Yacorzynski, G., and Fearing, F.: Further Evidence of Cerebellar Influence in the Habituation of After-Nystagmus in Pigeons, Am. J. Physiol. **120**:350 (Oct.) 1937.

37. Yacorzynski, G. K.; Halstead, W., and Fearing, F.: Relationship Between the Experimental Reduction of Vestibular Nystagmus and Equilibrium, J. Psychol. **11**:161 (Jan.) 1941.

38. Kisch, B.: A New Method to Produce Nystagmus, Exper. Med. & Surg. **1**:169 (May) 1943.

bodily equilibrium. They are spontaneous, not induced, and are usually of clinical significance.

1. *Nystagmus Originating in the Eye or Its Adnexa.*—(*a*) Nystagmus of Optic Derivation: The varieties of nystagmus in this group result from deficient vision, due either to impaired visual acuity or to inadequate illumination and retinal fatigue. The nystagmus is pendular rather than rhythmic in character, and the movements appear to result from an attempt to maintain fixation of vision in spite of deficient acuity or insufficient light. The nystagmus may appear in early infancy or may be acquired. It is not congenital in the sense of true congenital or hereditary nystagmus, to be described later.

(1) "Ocular" Nystagmus: This is of the pendular variety and is usually coarse and slow. The nystagmus is characterized by to and fro movements, often of equal range and velocity, toward each side of a central point. The movements may be wide and aimless and of the "wandering" or "roving" type. They may be quite irregular. They are usually horizontal, occasionally vertical and rarely rotatory. This type of nystagmus is seen in persons who have had very deficient vision since birth, in persons whose vision has failed before fixation is learned, in persons whose fixation is deficient, in color-blind persons or in persons with increased sensitivity to light. It is observed principally in persons with congenital cataract, ophthalmia neonatorum, interstitial keratitis, congenital corneal leukoma, chorioretinitis, high errors of refraction, especially high grade myopia, and albinism. The nystagmus develops shortly after birth, and it does not occur in persons who are blind from birth. It probably begins when the infant first attempts fixation. As a result of poor vision or imperfect macular vision, a "searching" movement of the eyes develops as the infant attempts to increase the incoming impulses, to find the sharpest image or to achieve adequate fixation. It is an adaptation to attain fixation in spite of defective vision. Sometimes there is an associated nodding of the head. It does not occur in adults unless macular vision is disturbed, and when the blindness is acquired later in life the movements are slower, wider in range and seemingly aimless; they are less rhythmic and probably do not constitute a true nystagmus, but they, also, represent attempts at fixation. Ocular nystagmus has been classified as that associated with amblyopia and that resulting from amaurosis, but there is no nystagmus associated with complete blindness. Unilateral nystagmus may occur with unilateral atrophy of the optic nerve or with other visual defects. An inconstant spontaneous nystagmus is sometimes seen with homonymous hemianoptic visual defects, particularly when the subject is looking to the blind side. This is probably not entirely ocular in origin, as it is usually of the rhythmic type and may vary with position. Some authorities believe that there may be a nystagmus associated with refractive errors without serious loss of vision.

(2) Occupational Nystagmus: This form results from eye strain due to deficient illumination, repeated movements of the eyes or retinal fatigue. It is a pendular nystagmus, fine in degree, rapid in rate, often vertical in direction and increased on upward gaze. The movements may not be conjugate. Fixation is also defective, and there may be spasm of the levator palpebrae superioris muscle. Occupational nystagmus is most frequently encountered in miners and other persons who work in poor light, and it is commonly referred to as "miner's nystagmus." It is also seen in compositors, draftsmen, jewelers, train dispatchers, crane workers, painters and others whose work necessitates movement of the eyes and strain on the ocular muscles or results in retinal fatigue.[39] It most often develops after long exposure to poor illumination, especially after working in a stooped attitude with the eyes deviated upward, and is probably the result of insufficiency of binocular fusion. Only the rods are used for vision in imperfect light, and as there are no rods at the macula there is inefficient macular vision in poor illumination. As a result there is a constant shifting of the axis of the eyes. After a time this shifting is present constantly, and not only in dim light. It is possible that there may be an associated vestibular component, inasmuch as the movements may be influenced by a change in the position of the head.[40] Some workers regard the phenomenon as a true neurosis, a result of "neuromotor exhaustion," and others postulate fatigue and toxic factors as of etiologic import. It may be that neurotic factors play a part in maintaining the nystagmus or in the production of symptoms, but deficient illumination, together with strain on the ocular muscles and retinal fatigue, seems to explain the phenomenon. Improved lighting, improved working conditions or cessation from work for

39. (*a*) Spicer, W. T. H., in Discussion on Nystagmus, Proc. Roy. Soc. Med. (Sects. Neurol., Ophth. & Otol.) **7**:20, 1913-1914. (*b*) Smith, H. C., and Riesenman, F. R.: Unusual Forms of Nystagmus, with a Review of the Literature, Arch. Ophth. **33**:13 (Jan.) 1945.

40. Duke-Elder,[2] p. 639.

a time may result in disappearance of the nystagmus, except the most severe form.

(3) Spamus Nutans: This condition is seen in babies from 6 months to 2 years of age. It consists in rhythmic nodding or rotatory tremor of the head accompanied with a fine, rapid, pendular type of nystagmus. The nystagmus is usually horizontal in direction, but it may be vertical. The movements may be unilateral or dissociated. Closing of the eyes stops the tremor and the nystagmus, while forceful control of the tremor increases the nystagmus. The condition has been ascribed to rickets, but it is known to occur in children who live in dark dwellings where no sunlight penetrates, regardless of the presence of rickets. The condition may be of complex origin, both ocular and central, but the cessation of the nystagmus on closing the eyes suggests that there is an ocular element in the causation of the disorder, perhaps similar to that in miner's nystagmus.

(4) Reflex Nystagmus: This form occurs in the presence of painful disease of the eye, is a pathologic variation of reflex sensory nystagmus and may also be considered to be of ocular derivation.

(*b*) Nystagmus of Neuromuscular Origin: In a large percentage of normal persons a few fine, rapid nystagmoid movements are seen on extreme deviation of the eyes. This is more noticeable on lateral gaze and is usually horizontal in direction. The rapid movement is in the direction of gaze and represents intermittent attempts of the agonists to maintain fixation. The slow return represents the reflex contraction of the overstretched antagonists in an attempt to return the eyes to the central position.[23] These movements are irregular and are usually transient; they may disappear gradually after five to ten jerks. This type of oscillation is sometimes referred to as *Endstellungsnystagmus,*[41] or "end position nystagmus," inasmuch as the movement is present only on extreme position of the eyes; but the terms "fixation nystagmus," "positional nystagmus" and "pseudonystagmus" are also used, and some authorities prefer to designate the movements as nystagmoid jerks, as they feel that the movements do not constitute a true nystagmus. The term *Endstellungsnystagmus* is not very appropriate, as end position nystagmus may be found with various pathologic states in which the movements are evident only on, or are exaggerated by, deviation of the eyeballs. These movements may occur in normal persons when they attempt to fix their eyes on an object without turning the head in the direction of the object or when they suddenly change the field of vision. The movements disappear when fixation has been established. The nystagmus may be the result of an abnormally great effort to balance the activity of the agonists and the antagonists. The tendency toward the phenomenon is increased with fatigue states, paresis of the ocular muscles and abnormal attempts at fixation and is often seen in nervous subjects. Exaggerations of this type of nystagmus are seen in the circumstances indicated in the following paragraphs:

(1) Paretic Nystagmus: This condition develops on the attempt to use a paretic ocular muscle. It is a rhythmic nystagmus, which occurs near the limit of the range of movement of a weak ocular muscle. When the subject is looking toward the paretic side, the weak agonist pulls the eyeball outward with a rapid jerk to avoid diplopia, and the antagonistic muscles slowly pull the eyeball back to the neutral position There may be dissociation between the movements of the paretic and those of the normal eye. One finds such a nystagmus in persons with localized extraocular palsies, but it may also occur with paresis of conjugate gaze.

(2) Fatigue Nystagmus: This is similar to paretic nystagmus. It may follow excessive use of or increased fatigability of certain extraocular muscles or may occur in generalized fatigue states or asthenia. It is usually observed only at extremes of lateral gaze and is generally abortive rather than sustained. It may occur when a subject attempts to hold his eyes in any extreme position for too long a period. In patients with myasthenia gravis one may observe nystagmus, which may be either of the paretic or of the fatigue variety.

(3) Nystagmus of Eccentric Fixation: This type appears on deviation of the eyes beyond the limits of the binocular visual field. It is jerky and rhythmic in type and horizontal in direction. It may occur without pathologic significance, and it is said to be present in 50 to 60 per cent of normal persons when the axes of fixation are deviated.[42] It is induced more readily by, or increased in, fatigue.

(4) Latent Nystagmus: This form appears on covering one eye in subjects with poor visual acuity or without binocular vision, especially patients with amblyopia resulting from strabismus. It occurs in the covered eye and is in the direction of the open eye.[43] Nystagmus of

41. Spiegel and Sommer,[3] p. 105.

42. Duke-Elder,[2] p. 636.

43. Duke-Elder,[2] p. 638.

eccentric fixation and latent nystagmus may be partially of ocular origin, inasmuch as they represent an attempt to aid vision, but the rhythmicity suggests neuromuscular factors in their causation.

(*c*) Opticokinetic Nystagmus: This form of nystagmus, especially if it is the result of a minimal stimulus, may be considered as a variety either of spontaneous nystagmus of ocular derivation or of nystagmus of neuromuscular origin. This illustrates the functional relationship of the various types of nystagmus. If the opticokinetic nystagmus is dependent on fixation and results from an attempt to maintain central, or macular, vision or to visualize more clearly the object that is in the field of vision, one may consider it of ocular origin; if it results from attempts at fixation on a moving object, from an effort to keep the eyes in one position or from tension on the ocular muscles, one may consider it of neuromuscular origin. While opticokinetic nystagmus is considered a physiologic response, a normal result of fixation of the eyes on moving objects, it may in certain circumstances be a pathologic variety of nystagmus. The tendency of certain persons to experience motion sickness, train sickness, air sickness and sea sickness may in part be due to a latent tendency toward the development of opticokinetic nystagmus. The related presence of an oversensitive vestibular or labyrinthine apparatus with these varieties of motion sickness indicates, however, that there are other factors than the ocular ones. This illustrates further the integrative action of the various portions of the nervous system in the production of nystagmus.

2. Nystagmus Due to Involvement of the Centers Controlling Ocular Movement and Equilibrium.—This type is, in most instances, true pathologic nystagmus. It is of diagnostic import in the presence of many diseases of the central nervous system. It must be stated, however, that certain varieties, while not actually physiologic, do not denote the presence of serious disease of the nervous system. The nystagmus of this general type is sometimes classified as cerebral (or central), cerebellar and vestibular; but, inasmuch as synthesis of the centers in the cerebrum which regulate ocular movements, the superior colliculus, the cerebellum, the nuclei of the ocular motor nerves, the medial longitudinal fasciculus and the vestibular apparatus is necessary for smooth and coordinated ocular movement, it is not always possible or feasible to differentiate the various subtypes. Unfortunately, the many varieties are often classified together as "central" nystagmus, but this terminology tells little regarding the etiologic factors or the site of pathologic change. Nystagmus due to involvement of the centers controlling ocular movement and equilibrium is rhythmic and may occur in any direction. It is similar in many respects to the induced nystagmus which is produced on stimulation of the labyrinth or the vestibular centers. It is of more significance if it is of the mixed or rotatory varieties or if there is dissociation of movement. The range and velocity of the movements may vary widely. The nystagmus may be spontaneous and present at rest; or it may be present only on fixation, at extremes of gaze or on change of the position of the head or body. Peter stated that nystagmus which is not the result of an ocular or an otologic factor is always the result of a lesion of the structures of the brain below the tentorium cerebelli,[44] but this is not true. The pathologic process may be in any of the following sites: (*a*) the cerebral cortex, especially the centers in the frontal, occipital and temporal regions which control ocular movement, and the central connections of the vestibular system; (*b*) the basal ganglia or the thalamus, in certain instances; (*c*) the corticofugal pathways from the oculogyric centers; (*d*) the superior colliculi (anterior quadrigeminal bodies); (*e*) the nuclei of the oculomotor, trochlear and abducens nerve; (*f*) the medial longitudinal fasciculus and its nuclear connections, involving this tract as far caudally as its termination in the cervical portion of the spinal cord; (*g*) the vestibular mechanism, including the labyrinth, the vestibular nerves, the vestibular nuclei and their central connections, and (*h*) the cerebellum and its connections with the spinal cord, the vestibular centers, the brain stem and the cerebrum.

(*a*) Vestibular Nystagmus: Vestibular nystagmus is a reflex response to stimulation or destruction of the labyrinth. The afferent impulse passes from the labyrinth to the area of the vestibular nuclei and thence to the nuclei of the ocular muscles, and the efferent, or motor, path goes to the individual muscles. Stimulation of the labyrinth, of specific semicircular canals, of the vestibular nerves or of the vestibular nuclei by a toxic process, pressure, edema or inflammation produces essentially the same type of response as does stimulation of these centers by rotation, heat or cold or the galvanic current, and the response depends on the type of stimulus and the part of the vestibular system that is stimulated. It has been stated that the horizontal canals are responsible mainly for horizontal nystagmus, the posterior vertical canals for vertical nystagmus and the anterior vertical canals for rotatory nystagmus. Each labyrinth

44. Peter,[1] p. 307.

has connections with all the ocular muscles of each eye. The pathologic process may cause a unidirectional flow of the endolymph, or it may stimulate the nerve endings or the nuclei directly. Destruction of one labyrinth or of one vestibular nerve results in a rhythmic, spontaneous nystagmus the slow phase of which is toward the injured side,[23] and there may be associated deviation of the eyes and head toward this side. The labyrinths are antagonistic to each other, so that elimination of one acts as a stimulus to the other. The amplitude of the nystagmus is increased by turning the eyes in the direction of the quick phase or by the elimination of fixation by placing strong lenses in front of the eyes.[23] The direction of the nystagmus may be reversed by altering the position of the head. Nystagmus which follows destruction of one labyrinth gradually diminishes and disappears. It may last only two or three days and is usually gone in a week, as the loss of one labyrinth is compensated for by processes in the corresponding vestibular nuclei.[45] The nystagmus which appears after destruction of one labyrinth disappears if the other labyrinth is rendered functionless.

Hemorrhage into the labyrinth; suppuration of the labyrinth secondary to disease of the middle ear; increased or decreased pressure of the labyrinthine fluid; pressure on the inner ear; trauma to the vestibular nerve as a result of skull fracture; intracranial hemorrhage; meningitis; involvement of the vestibular nerve by a neoplastic process, such as a neurinoma of the cerebellopontile angle, or toxic or inflammatory involvement of the labyrinth or the nerve will result in nystagmus, which may be temporary or persistent. The nystagmus associated with toxic labyrinthitis may result from stimulation of the vestibular end organs by the toxic process, or it may be of the compression variety, resulting from increased pressure of the labyrinthine fluid in the semicircular canals. In patients with Ménière's syndrome the nystagmus may result from increased secretion of the endolymph on an allergic basis, or it may be due to change in the acid-base or the electrolyte balance. In patients with disease of the middle ear nystagmus may be produced by sudden compression of the external auditory meatus. It may be possible to differentiate between nystagmus due to irritation and that due to destruction of the labyrinth by caloric stimulation of the external auditory canal. With the former the nystagmus will be increased, whereas with the latter no reflex nystagmus will be elicited and there will be no change in the nystagmus which is already present. With many disease processes, such as tumors of the cerebellopontile angle, multiple sclerosis and lesions of the pons and medulla, vestibular nystagmus may be complicated by the existence of nystagmus due to involvement of the cerebellum, the medial longitudinal fasciculus or other structures.

(*b*) Nystagmus of Cerebellar Origin: This may be an ocular expression of cerebellar asynergia or ataxia, a result of synergic disorders of fixation of cerebellar origin; it may be due to involvement of the cerebellar connections with the vestibular apparatus, the medial longitudinal fasciculus or higher centers, or it may be a specific manifestation of cerebellar dysfunction. Nystagmus is a common symptom in patients with cerebellar lesions, regardless of whether they are traumatic, vascular, degenerative, inflammatory or neoplastic in nature, and it may occur with lesions of the vermis, of the hemispheres, either cortical or subcortical, or of the cerebellar peduncles and their connections. With unilateral ablation of the cerebellum in animals, coarse, slow jerks occur when the eyes are directed to the side of the lesion, and rapid and finer jerks, when the eyes are directed to the opposite side. With lesions of the cerebellum, the eyes at rest are deviated 10 to 30 degrees toward the unaffected side.[23] The movements may be present on fixation or on deviation in any direction. When the subject attempts to focus on an object directly in front of him, the eyes wander slowly back to the resting position and are returned to the midline by means of quick jerks. On his looking toward either side, there are quick jerks toward the point of fixation with slow return movements to the resting point. The rapid movements are always in the direction of gaze, and the slow movements are toward the position of rest. The nystagmus is always more pronounced when the subject is looking toward the side of the lesion.

It has often been stated that nystagmus develops in patients with cerebellar lesions only as a result of the effect of the lesion on the vestibular centers through pressure and edema, but this obviously is not the case. It may be that the cerebellum has an inhibitory effect on nystagmus, inasmuch as the phenomenon develops after ablation of the cerebellum and removal of one hemisphere results in an increase in nystagmus toward the side of the lesion. Spiegel produced vertical nystagmus by means of lesions in the nodulus or other parts of the vermis. He expressed the belief that this may be the result of the release of the vestibulo-ocular reflex arcs from cerebellar inhibition.[45] Pigeons with cerebellar lesions do

45. Spiegel, E. A., and Scala, N. P.: The Significance of Nystagmus in Differential Diagnosis, with Special Reference to Vertical Nystagmus, Tr. Am. Therap. Soc. **42**:60, 1942.

not become habituated to nystagmus as readily as do controls.[36] It is probable, however, that irritation of this portion of the central nervous system also produces nystagmus. The exact site of damage is often difficult to determine because of the multiplicity of connections with the vestibular, oculogyric and other centers. It is said that cerebellar nystagmus is dependent on fixation, in contrast to vestibular nystagmus, which is increased when fixation is eliminated by the use of strong lenses.[23] In vestibular nystagmus the slow phase is toward the injured side, while in cerebellar nystagmus the slow phase depends on the position of the eyes.[23]

(*c*) "Central" Nystagmus: "Central" nystagmus may result from lesions of the oculogyric centers in the frontal, occipital or temporal lobe; central involvement of vestibular function in the temporal lobe, or involvement of the descending pathways from the volitional oculogyric center in the frontal lobe or of the corticofugal fibers from the occipital lobe, the medial longitudinal fasciculus and its connections or the nuclei of the nerves which control ocular movement. It may vary in type, degree, rate and direction but is always of the rhythmic variety. With central lesions there is often a dissociation of movement, with unequal nystagmus on the two sides or with unilateral nystagmus. This is especially true if the disease process is in the brain stem. Spontaneous vertical nystagmus is said to be characteristic of intracranial disease because it is dependent for its production on the simultaneous stimulation of both posterior or of both anterior vertical semicircular canals, or of the pathways connecting them, the last-named being the most likely site. It has been stated that spontaneous vertical nystagmus is an infallible and pathognomonic sign of a pathologic lesion of the brain,[46] although Spiegel and Scala[47] produced such nystagmus by peripheral labyrinthine lesions.

Cerebral lesions may cause spontaneous nystagmus, or they may influence or alter the induced opticokinetic or labyrinthine nystagmus. In patients with cerebral lesions the nystagmus is usually of the fixation type and is probably an exaggeration of positional nystagmus when the eyes are deviated away from the side of the lesion.[23] An inconstant nystagmus is sometimes seen with homonymous hemianoptic defects, particularly when the subject is looking to the blind side. It has been stated that cerebral lesions, especially if destructive, may abolish the quick phase of the nystagmus, but it is now known that the quick phase is not necessarily a cerebral function. In most instances cerebral nystagmus is the result of suspension of the inhibitory action of the cortex on the centers of ocular movement.[48] For localization of the lesion that causes nystagmus of a central type, one must rely on associated signs and symptoms. Associated paresis of upward gaze may suggest mesencephalic involvement, while conjugate paresis of lateral gaze may suggest cortical or pontile involvement. Paresis of conjugate lateral gaze with associated paralysis of individual muscles places the lesion near the nuclei of the cranial nerves involved.

Nystagmus that results from involvement of the supranuclear or association pathways is found with many diseases of the nervous system, among which may be mentioned multiple sclerosis, Friedreich's ataxia, Marie's hereditary ataxia, olivopontocerebellar atrophy, syringobulbia, syringomyelia and vascular, neoplastic or degenerative diseases of the brain stem. It is often impossible to state whether the primary disease process is cerebral or is in the brain stem, the cerebellum or the connecting pathways, and in many instances, as in encephalitis, multiple sclerosis and toxic processes, it is disseminated. Harris has recently described an "ataxic nystagmus" which he states is a pathognomonic sign of multiple sclerosis.[49] When the eyes are turned laterally, it is seen that the conjugate action is weak, and the opposite eye does not reach the inner canthus. The eye on the side toward which the eyes are being turned shows a coarse nystagmus, with the quick movement in the direction of gaze and a slow return movement. The nystagmus continues as long as the eyes are deviated. This type of nystagmus may be unilateral; it may be present on looking in either direction, or it may be disproportionate. The nystagmus associated with multiple sclerosis may, however, vary greatly in individual cases, depending on the site of the pathologic change.

3. *Miscellaneous Varieties of Nystagmus.*—(*a*) Toxic Nystagmus: This type may be associated with definite disease of the nervous system, but oftentimes it is the only objective manifestation of the ingestion of certain drugs, especially the barbiturates,[38] acetanilid and related drugs, diphenylhydantoin, lead, nicotine, chloroform,

46. Fisher, L., and Glaser, M. A.: New Vestibular Complexes for Localization of Brain Lesions, Arch. Neurol. & Psychiat. **21**:876 (April) 1929.

47. Spiegel, E. A., and Scala, N. P.: Vertical Nystagmus Produced by Peripheral Labyrinthine Lesions, Arch. Otolaryng. **40**:160 (Sept.) 1944.

48. Rea, R. L.: Neuro-Ophthalmology, ed. 2, St. Louis, C. V. Mosby Company, 1941, p. 67.

49. Harris, W.: Ataxic Nystagmus: A Pathognomonic Sign in Disseminated Sclerosis, Brit. J. Ophth. **28**:40 (Jan.) 1944.

quinine and alcohol. It is also found during the febrile state of acute infectious diseases. The site of the damage may vary. With toxic labyrinthitis it is localized to the labyrinths, but the toxic process may involve other parts of the nervous system. The nystagmus that is seen in persons with epilepsy may be a result of the disease process underlying the convulsive disorder, or it may be a toxic nystagmus, a result of the anticonvulsant medication.

(*b*) Congenital or Hereditary Nystagmus: This form, which dates from birth, must be differentiated from ocular nystagmus, which does not develop until fixation is attempted. Furthermore, it is rhythmic and more rapid and is not associated with defective vision. It may be inherited along mendelian lines and is probably the result of a congenital abnormality or hypoplasia of the central nervous system. It has been stated that hereditary nystagmus may be an autosomal recessive trait; it may be sex linked, occurring only in males, or it may be irregularly dominant, occurring in both sexes.[50] It may be associated with partial albinism.

(*c*) Nystagmus Due to Involvement of the Cervical Portion of the Spinal Cord: The lesion is usually above the fourth cervical segment, as in cases of syringomyelia and tumors of the cervical part of the cord. The nystagmus is "central" in that it indicates involvement of the medial longitudinal fasciculus or the spinocerebellar or vestibulospinal pathways. There may be some relationship between the tonic neck reflexes and their effect on ocular movement and the nystagmus which results from cervical lesions.

(*d*) Hysterical Nystagmus: Many authorities have described hysterical varieties of nystagmus. The actual existence of such a type is to be doubted, but if it does occur it may be the result of inadequate neuromuscular control of the lateral movements of the eyes and failure of alternate contraction of the agonists and antagonists on deviation of the eyes. The movements are usually described as jerky and irregular, but they may be pendular.[51] They may be brought on by emotional strain, but it must be borne in mind that a true pathologic nystagmus may be increased by nervous tension and that nervous and fatigued persons are especially apt to show nystagmoid movements or fixation nystagmus when they attempt to fix their eyes on some object with extreme deviation. With so-called hysterical nystagmus there may be associated spasm of the orbicularis oculi and medial rectus muscles.

(*e*) Voluntary Nystagmus: Such a form has also been described, and nystagmus can occasionally be simulated. Voluntary nystagmus is usually pendular, and it may be unilateral or bilateral.[39b] The movements are extremely rapid; they are usually horizontal but may be in any direction. The movements are increased by fixation, by convergence or by increasing the width of the palpebral fissure.[52] The nystagmus disappears when the subject's attention is distracted or when vision is blurred by a convex lens placed in front of each eye. The movements are said to be produced at will, and they are not associated with any pathologic entity. It is doubtful whether these voluntary movements of the eyeball should be considered as a type of nystagmus.

University Hospital.

50. Allen, M.: Primary Hereditary Nystagmus: Case Study with Genealogy, J. Hered. **33**:454 (Dec.) 1942.

51. Smith and Riesenman.[39b]

52. Unsworth, A. C.: A Discussion of Ocular Malingering in the Armed Services, Am. J. Ophth. **28**: 148 (Feb.) 1945.

ONSET OF GUILLAIN-BARRÉ SYNDROME FOLLOWING EXPOSURE TO MUSTARD GAS

CAPTAIN JOSEPH G. CHUSID
AND
COLONEL GILBERT H. MARQUARDT
MEDICAL CORPS, ARMY OF THE UNITED STATES

The clinical incidence of neurologic sequelae of mustard gas poisoning or exposure is rare. Mustard gas, the popular name of dichloroethyl sulfide, was known during World War I as "king of battle gases," [1] inasmuch as, pound for pound, it produced nearly eight times the number of casualties produced by all the other battle gases combined. Marshall [2] concluded that systemic effects occurred in animals, due in part to absorption of mustard gas or a hydrolytic product thereof, when these animals were poisoned by inhalation, injection or cutaneous application of this substance. Winternitz [3] stated that animals which died in the acute stage, before the development of extensive pneumonia, probably succumbed as a result of the combined effects of destructive changes in the lung and systemic effects from absorption of the gas. Warthin [4] mentioned the following signs referable to the central nervous system in animals exposed to mustard gas vapor: increased reflex excitability, tremors, convulsions, marked depression, stupor and coma. His examination of the brain and spinal cord of rabbits and of 1 human being disclosed congestion and edema throughout. Gilchrist and Matz [5] reviewed the clinical status of 89 persons living who had previously been exposed to mustard gas during World War I and of 53 who had died as a result of such exposure and concluded that mustard gas affected particularly the skin, the mucous membranes of the upper portion of the respiratory tract and the eyes and their appendages and that secondary bronchopneumonia was a frequent complication and cause of death following mustard gas poisoning. No organic neurologic sequelae were noted.

The term Guillain-Barré syndrome has been used to designate that type of polyneuritis occurring with albuminocytologic dissociation and characterized clinically by acute onset, mild or no febrile reaction, radicular neuritis, palsy of the cranial nerves and muscular tenderness.[6] The syndrome has been called by others acute infectious polyneuritis,[7] polyneuritis with facial diplegia,[8] polyradiculoneuritis,[9] infectious neuronitis [10] and myeloradiculitis.[11] Attempts to isolate or identify the infectious agent have generally been unsuccessful.[12] The possible rela-

From the Neurology Section of the Medical Service, AAF Regional and Convalescent Hospital, Miami District, Miami Beach, Fla.

1. Prentiss, A. M.: Chemicals in War, New York, McGraw-Hill Book Company, Inc., 1937.

2. Marshall, E. K., Jr.: Physiological Action of Dichloroethyl Sulphide, in Ireland, M. W.: The Medical Department of the United States Army in the World War: Medical Aspects of Gas Warfare, Washington, D. C., Government Printing Office, 1926, vol. 14, p. 369.

3. Winternitz M. C.: Pathology of War Gas Poisoning, New Haven, Conn., Yale University Press, 1920.

4. Warthin, A. S.: Pathologic Action of Mustard Gas, in Ireland, M. W.: The Medical Department of the United States Army in the World War: Medical Aspects of Gas Warfare, Washington, D. C., Government Printing Office, vol. 14, p. 512.

5. Gilchrist, H. L., and Matz, P. B.: The Residual Effects of Warfare Gases: I. Chlorine; II. Mustard, War Department, Chemical Warfare Service, Washington, D. C., Government Printing Office, 1933.

6. Roseman, E., and Aring, C. D.: Infectious Polyneuritis, Medicine **20**:463, 1941. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis, ibid. **35**:937 (May) 1936.

7. De Sanctis, A. G., and Green, M.: Acute Infectious Polyneuritis, J. A. M. A. **118**:1445 (April 25) 1942.

8. Forster, F. M.; Brown M., and Merritt, H. H.: Polyneuritis with Facial Diplegia, New England J. Med. **215**:51, 1941.

9. Garvey, P. H.; Jones, N., and Warren, S. L.: Polyradiculoneuritis (Guillain-Barré Syndrome) Following Use of Sulfanilamide and Fever Therapy, J. A. M. A. **115**:1955 (Dec. 7) 1940.

10. Kennedy, F.: Infectious Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919.

11. Strauss, I., and Rabiner, A. M.: Myeloradiculitis, Arch. Neurol. & Psychiat. **23**:240 (Feb.) 1930.

12. Aring, C. D., and Sabin, A. B.: Fatal Infectious Polyneuritis in Childhood, Arch. Neurol. & Psychiat. **47**:938 (June) 1942. Honeyman, W. M.: Pathological Study of a Group of Cases Sometimes Referred to as

(Footnote continued on next page)

tionship to preceding infection of the upper respiratory tract,[11] hyperthermia [9] and infection of the gastrointestinal tract [13] has been noted.

The onset of the Guillain-Barré syndrome after mustard gas poisoning or exposure may theoretically follow as a consequence of the local effects of mustard gas on the upper respiratory tract,[14] the gastrointestinal tract,[2] the skin [2] or the central nervous system [2]; in the preceding circumstances, "activation" of a virus present in the locally affected tissue may have occurred as a result of the local changes induced by this poison or its breakdown products. The activation may represent an actual increase in potency of the virus, a decrease in local powers of resistance or a combination of the two factors.

REPORT OF A CASE

The patient, a "toxic gas handler," served as an enlisted man in the Chemical Warfare Service in India. On July 1, 1944 he was accidentally exposed to mustard gas, which was emanating from a decontamination pit explosion 15 feet (4.5 meters) away. The patient immediately recognized the smell of mustard gas and removed his clothes, which were subsequently washed and laundered. He was not aware of lacrimation, coughing or sneezing immediately after the exposure, and he considered that in general he had suffered no ill effects. On July 5 he again wore the trousers which had been contaminated and continued to wear them for three days. By July 10 or 12 severe erythema, blistering and ulceration of both legs and thighs were apparent. Admission to a station hospital followed, and there, under local treatment, the ulcerated areas became relatively clean, so that on August 18 skin grafts were applied to these areas, with the patient under spinal anesthesia. Casts were applied from just above the knees down to the feet after operation. On August 24 the patient was allowed out of bed, but when he attempted to walk he found it difficult to support himself on his legs. For the next month the patient contented himself with sitting up in a chair and walking very short distances with the aid of a cane. Neurologic examination, on September 24, was reported to show absence of deep reflexes, generalized weakness of the arms and legs and ataxia in performance of the finger to nose test bilaterally. The cerebrospinal fluid at this time showed 6 lymphocytes per cubic millimeter and 114 mg. of total protein per hundred cubic centimeters. Two days later neurologic examination showed impairment of the sense of touch in both lower extremities, loss of appreciation of vibration and position in both knees and feet and marked ataxia in the finger to nose and heel to knee tests. Repeated examinations of the cerebrospinal fluid on October 5 showed 1 polymorphonuclear cell per cubic millimeter and 156 mg. of total protein per hundred cubic centimeters. On October 13 clinical progression of the disease was evidenced by the greater weakness in the lower limbs, complete lack of position sense, absence of cremasteric reflexes, weak abdominal reflexes and absence of deep reflexes. On October 14 the cerebrospinal fluid showed 1 polymorphonuclear cell and 1 lymphocyte per cubic millimeter and 281 mg. of total protein per hundred cubic centimeters. The patient now complained of stiffness and aching of the arms, forearms and hands, and he found it difficult to button his clothes. On November 6 he was admitted to this hospital. Neurologic examination revealed moderate atrophy of the musculature of the hands and both lower extremities, absence of deep reflexes and a mild to moderate degree of weakness in the extensors and abductors of both shoulders, the abductors of the left thigh, the dorsiflexors of both feet and the extensors of both wrists. The patient could walk only a few steps, and this with the aid of two canes. A complete blood count and urinalyses revealed normal constituents, and the results of examinations of stools for amebas and parasites and repeated nasopharyngeal cultures for diphtheria bacilli were negative. The Schick test gave a negative reaction. The roentgenogram of the chest, the electrocardiogram and the electroencephalogram were normal. On November 11 the cerebrospinal fluid was under a pressure of 140 mm. of water and showed 14 lymphocytes per cubic millimeter and 119 mg. of total protein per hundred cubic centimeters; the Wassermann reaction was negative, and the colloidal gold curve was 0001111110. The patient was placed on a high calory, high vitamin diet and received intensive physical therapy in the form of massage, heat and muscle reeducation. Within six weeks he had completely regained his strength. On December 22 the cerebrospinal fluid was under a pressure of 185 mm. of water, and examination showed 10 lymphocytes per cubic millimeter, 48 mg. of total protein per hundred cubic centimeters and a colloidal gold curve of 0122221000. The patient was discharged to duty on Jan. 13, 1945, at which time he had gained 20 pounds (9.1 Kg.) in weight and was neurologically normal except for the continued absence of deep reflexes.

SUMMARY

A case of the Guillain-Barré syndrome, with onset after exposure to mustard gas, is reported. The activation of the disease by changes induced in the skin, the respiratory tract, the gastrointestinal tract or the central nervous system is considered as a probable mechanism of action.

Polyneuritis, Bull. Neurol. Inst. New York **6**:519, 1937. Sabin, A. B., and Aring, C. D.: Visceral Lesions in Infectious Polyneuritis, Am. J. Path. **17**:469, 1941.

13. Chusid, J. G., and Marquardt, G. H.: Acute Infectious Polyneuritis (Guillain-Barré Type), Ann. Int. Med., to be published.

14. Winternitz.[3] Gilchrist and Matz.[5]

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

At the annual meeting of the American Board of Psychiatry and Neurology the following officers were elected: president, Dr. John C. Whitehorn; vice president, Dr. Percival Bailey; secretary-treasurer, Capt. Francis J. Braceland.

It was voted to amend the by-laws so as to discontinue certification on record as of Jan. 1, 1947.

The next examination will be held before the meeting of the American Psychiatric Association in Chicago on May 24 and 25, 1946, and before the meeting of the American Neurological Association in San Francisco, June 26, 1946, provided at least 40 candidates appear. The list of diplomates certified in December 1945 follows:

Neurology and Psychiatry.—By Examination: Capt. Sidney Berman, M.C., A.U.S. (formerly Detroit); Major Winston I. Breslin, R.C.A.M.C. (formerly Chicago); Willard C. Brinegar, Concord, N. H.; Alice Boole Campbell, New York; Arthur Attilio Clinco, Brooklyn; Lieut. Joseph L. Cummings (MC), U.S.N.R. (formerly Poughkeepsie, N. Y.); Charles Fisher, Ellis Island, N. Y.; Major Herbert S. Gaskill, M.C., A.U.S. (formerly Philadelphia); Capt. Martin Jerome Gerson, M.C., A.U.S. (formerly Howard, R. I.); Paul H. Hoch, New York; Samuel P. Hunt, Oakland, Calif.; Capt. Max Edwards Johnson, M.C., A.U.S. (formerly Washington, D. C.); Charles Joseph Katz, Elgin, Ill.; Sidney Levin, Boston; Wilmot S. Littlejohn, Birmingham, Ala.; Hans Lowenbach, Durham, N. C.; Bruce R. Merrill, Bronxville, N. Y.; Capt. Herbert C. Modlin, M.C., A.U.S. (formerly Boston); Major Benedict Nagler, M.C., A.U.S. (formerly Newark, N. J.); Harold H. Noran, Minneapolis; Abe Pinsky, Brooklyn; Leon Roizin, New York; Joseph E. Rubinstein, New York; Capt. Leon Marcus Simms, M.C., A.U.S. (formerly Brooklyn); Capt. Charles O. Sturdevant, M. C., A.U.S. (formerly Portland, Ore.); George N. Thompson, Los Angeles; John Baer Train, New York; Lieut. Walter Irvin Tucker (MC), U.S.N.R. (formerly Belmont, Mass.); Montague Ullman, Brooklyn; George D. Weickhardt, Washington, D. C.; Capt. Frederick G. Woodson, M.C., A.U.S. (formerly Charlottesville, Va.).

Neurology and Psychiatry.—On Record: Ralph Edward Davis, Boise, Idaho; Robert L. Dixon, Caro, Mich.; Ernst Lewy, Topeka, Kan.

Psychiatry.—By Examination: Alan B. Adam, M.C., A.U.S. (formerly Cleveland); Lieut. Col. Freeman Hornibrook Adams, M.C., A.U.S. (formerly Washta, Iowa); Capt. Morris Harold Adler, O.R.D., A.U.S. (formerly Flushing, N. Y.); Abraham H. Ascher, Brooklyn; Alfred K. Baur, Washington, D. C.; Ralph Brancale, Attica, N. Y.; *Thomas C. Carey, Hartford, Conn.; Comdr. Raymond Stanley Clark, U.S.N. T.C. (formerly Los Angeles); Robert B. Clarke, Ann Arbor, Mich.; Louis Allan Cohen, Little Rock, Ark.; Sidney Drobnes, Norwich, Conn.; Capt. Herbert A. Duncan, M.C., A.U.S. (formerly Baltimore); Capt. Marcus Brown Emmons, M.C., A.U.S. (formerly Iowa City); Abraham A. Fabian, New York; Dora Fishback, Chicago; Fritz Adolf Freyhan, Farnhurst, Del.; Douglas Goldman, Cincinnati; Lieut. (jg) Sidney Lewis Green (MC), U.S.N.R. (formerly New York); Harold A. Greenberg, Chicago; Milton Greenblatt, Boston; Major Bernard L. Greene, M.C., A.U.S. (formerly Chicago); Werner Hochstetter, New York; Roger William Howell, Ann Arbor, Mich.; Paul E. Huston, Iowa City; Ralph B. Jacoby, Brentwood, N. Y.; Joseph G. Kepecs, Chicago; Edward Fox Kerman, Sykesville, Md.; Comdr. Henry Ambrose Kildee, M.C.-V(S), U.S.N.R. (formerly Roanoke, Va.); Major Paul Kramer, M.C., A.U.S. (formerly Chicago); Samuel R. Lehrman, New York; Lieut. Comdr. William Taylor Lhamon (MC), U.S.N.R. (formerly New York); Samuel Liebman, Winnetka, Ill.; Harry B. Luke, West Brentwood, N. Y.; Capt. S. Albert Molle, M.C., A.U.S. (formerly Toledo, Ohio); Claude Linwood Neale, Richmond, Va.; Max Needleman, New York; Douglas Noble, Washington, D. C.; Samuel Novey, Baltimore; Lieut. Lucy D. Ozarin, U.S.N.R. (formerly Helmuth, N. Y.); Ferdinand R. Pitrelli, Central Islip, N. Y.; George E. Poucher, M.C., A.U.S. (formerly Chicago); John J. Prusmack, M.C., A.U.S. (formerly Clarinda, Iowa); Major Leon L. Rackow, M.C., A.U.S. (formerly Roanoke, Va.); Angelo J. Raffaele, Willard, N. Y.; *Capt. Harold Ribner, M.C., A.U.S. (formerly Bridgeport, Conn.); Capt. George A. Rickles, M.C., A.U.S. (formerly Seattle); Herman Rickless, Westborough, Mass.; Capt. Hector J. Ritey, M.C., A.U.S. (formerly North College Hill, Ohio); Major William Laray Roach, Med. Br., W.D.P.C.; Martin H. Robinson, Philadelphia; Lieut. Comdr. Alan Roos (MC), U.S.N.R. (formerly Ridgefield, Conn.); Capt. Lawrence J. Roose, M.C., A.U.S. (formerly Orangeburg, N. Y.); William Byron Rossman, Ellettsville, Ind.; Capt. William P. Shelton, M.C., A.U.S. (formerly Kansas City, Mo.); Capt. Samuel Silverman, M.C., A.U.S. (formerly New York); Capt. Werner Simon, M.C., A.U.S. (formerly Palo Alto, Calif.); Alice Slater, Elmhurst, N. Y.; George K. Swartz, Norristown, Pa.; Comdr. J. Peter Thornton, M.C.-V(S), U.S.N.R. (formerly Boston); John H. Trevaskis, New York; Major Philip Sigmund Wagner, M.C., A.U.S. (formerly Fresno, Calif.); *Albert L. Wanner, Wheeling, W. Va.; Edward K. Wilk, Middletown, Conn.; Katherine W. Wright, Chicago; *Howard Zeitlin, Chicago; Marion Estelle Zonnis, Petersburg, Va.

Psychiatry.—On Record: Harry Shook Blossom, Patton Calif.; Chester Lee Carlisle, Palo Alto, Calif.; Jewel Fay, Berkeley, Calif.; Ina Moore Freshour, Norwalk, Calif.; Lieut. Col. Charles W. Grady, M.C., A.U.S. (formerly Palo Alto, Calif.); Earle Vincent Gray, Helmuth, N. Y.; Wirt Clarence Groom, Poughkeepsie, N. Y.; George W. Henry, New York; Richard T. O'Neil, Northampton, Mass.; Love Elree Pennington, Milledgeville, Ga.; Veronica Murphy Pennington, Milledgeville, Ga.; Robert Clarence Robertson, Dayton, Ohio; George Wilse Robinson, Kansas City, Mo.; Major John Walter Wills, M.C., A.U.S. (formerly Palo Alto, Calif).

Neurology.—By Examination: *Matthew Brody, Brooklyn; *Gerhard Chrzanowski, West Brentwood, N. Y.; *Lieut. Col. Ralph T. Collins, M.R.C. (formerly Mamaroneck, N. Y.); Lieut. Comdr. Stanley M. Dillenberg, M.C.-V(S), U.S.N.R. (formerly New York); *Franklin Smith Dubois, New Canaan, Conn.; Arnold Phineas Friedman, New York; *Nicholas G. Frignito, Philadelphia; *Joseph Julian Gitt, St. Louis; *Major Arthur J. Lapovsky, M.C., A.U.S. (formerly Brooklyn); *Alan A. Lieberman, Elgin, Ill.; Capt. Samuel Clements Little, M.C., A.U.S. (formerly Ann Arbor, Mich.); Herman Arnold Meyersburg, U.S.N. Training and Distributing Center (formerly Charlottesville, Va.); *Major Irvin I. Schatz, M.C., A.U.S. (formerly Pueblo, Colo).

Neurology.—On Record: *Lieut. Col. Harold E. Foster, M.C., A.U.S. (formerly Northport, N. Y.).

*The asterisk indicates complimentary certification.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Physiology

AN EXPERIMENTAL ANALYSIS OF THE INFERIOR MESENTERIC PLEXUS. ALBERT J. HARRIS, J. Comp. Neurol. **79**:1 (Aug.) 1943.

Harris made 3 series of experiments on the different nerves connected with the inferior mesenteric plexus in the cat in order to determine the origin of the fibers connected with the plexus and their number. After cutting the nerves, twenty-five to twenty-nine days were allowed for degeneration of the divided nerve fibers before the animals were killed. Two specimens were taken from each of three nerves, viz., the inferior mesenteric, the hypogastric and the intermesenteric. The intermesenteric nerves run between the aortic plexus and the inferior mesenteric ganglia and are composed of the fibers of the lumbar splanchnic nerves and fibers which come from higher levels in the aortic plexus. Half the samples were fixed in osmium tetroxide, and the other half were prepared by the Bodian protargol (strong protein silver) method to show both myelinated and unmyelinated fibers. The intact fibers were counted under an oil immersion lens. Twenty anatomic dissections were also made.

Harris found that about 4,000 preganglionic sympathetic fibers entered the inferior mesenteric ganglia. Of these, about 1,000 extended into the pelvis via the hypogastric nerves. On the average, 3,250 postganglionic fibers entered the ganglia from the sympathetic trunk and 6,500 postganglionic fibers originated in the inferior mesenteric ganglia. The visceral afferent fibers numbered approximately 5,000 on the distal side of the ganglia and 2,500 on the proximal side. This difference is explained on the assumption that the afferent fibers, on the average, each give rise to one collateral.

ADDISON, Philadelphia.

AN EXPERIMENTAL STUDY OF THE DEVELOPMENT OF THE MEDIAL LONGITUDINAL FASCICULUS IN THE CHICK. RUTH RHINES, J. Comp. Neurol. **79**:107 (Aug.) 1943.

Rhines attempted an analysis of the various components of the medial longitudinal fasciculus as development proceeded in early chick embryos. At the end of three hours' incubation she examined the brains of 18 chick embryos on which she had not operated and operated on 37 others of the same age. The operation consisted in removing variable amounts of the rostral end of the brain tube by means of a hair loop and allowing the embryos to continue incubation until 4 to 6 days of age. In 2 chick embryos a gap was made in the midbrain, and in 3 embryos the brain was divided at the level of the otocyst. The embryos were prepared by a pyridine silver method to show the nerve fibers. After four days of incubation fibers from the interstitial nucleus in the diencephalon descended homolaterally in the upper portion of the midbrain and overlapped with ascending fibers from nuclei situated near the sulcus limitans in the trigeminal region. Vestibular fibers began to contribute to the caudal end of the medial longitudinal fasciculus at 3 days of age. Descending vestibular fibers reached the upper vagus region. Spontaneous motility, like that of intact embryos, was seen at 5 days in all types of embryos which had been operated on. Rhines concludes that in the chick early spontaneous movements are not dependent on centers rostral to the mesencephalon.

ADDISON, Philadelphia.

THE ASCENDING AUDITORY PATHWAY IN THE BRAIN STEM OF THE MONKEY. W. T. BARNES, H. W. MAGOUN and S. W. RANSON, J. Comp. Neurol. **79**:129 (Aug.) 1943.

The authors studied the brains of 10 monkeys in which different parts of the auditory system had been destroyed. The lesions were made in the cochlear nuclei of 4 animals, in the superior olivary complex of 2, in the nucleus of the lateral lemniscus of 2 and in the inferior colliculus of the midbrain of 2. The brains were removed two weeks after operation, and serial sections were prepared by the Marchi method. The sections showed three distinct transverse striae—dorsal; intermediate, and ventral, or trapezoid body. The dorsal stria took origin in the dorsal cochlear nucleus and traversed the reticular formation ventral to the medial longitudinal fasciculus; thus it did not have a superficial position in the floor of the fourth ventricle, as described for man. The intermediate and ventral striae began in the ventral cochlear nucleus. A large number of fibers in all three striae synapsed in the contralateral superior olivary complex with neurons which ascended in the lateral lemniscus. Many other fibers of all three striae converged after crossing, turned at right angles in a rostral direction and ascended in the lateral lemniscus. A considerable number of fibers from the cochlear nucleus of one side synapsed in the homolateral superior olivary complex and began a homolateral acoustic pathway. The succeeding relay stations, where synapses of part of the fibers occurred, were the nucleus of the lateral lemniscus, the nucleus of the inferior colliculus and the medial geniculate body. The end station in each hemisphere was in the anterior transverse temporal gyrus of the cerebral cortex.

ADDISON, Philadelphia.

POLYDACTYLY AND ANTERIOR HORN CELLS IN FOWL. LISBETH BAUMANN and WALTER LANDAUER, J. Comp. Neurol. **79**:153 (Aug.) 1943.

Baumann and Landauer made counts of the motor nerve cells in the lumbosacral region of 8 adult fowls which had five toes on one foot and four toes on the other. For comparison, they studied 2 fowls with five toes on each foot, and 3 fowls with the normal number, four, on each foot. In the fowl the motor cells of the lumbosacral region may be grouped in six columns, and of these the cells of the dorsolateral and retrodorsolateral columns furnish most of the innervation of the leg and foot. The cell counts in these columns showed always a greater number of motor cells on the side with the extra toe. The authors consider that the asymmetry in the numbers of motor neurons occurs in consequence of hereditary asymmetries in peripheral structures.

ADDISON, Philadelphia.

Anatomy and Embryology

THE CONVOLUTED VESSELS OF BRAIN AND SPINAL CORD. RUDOLPH ALTSCHUL, J. Neuropath. & Exper. Neurol. **3**:386 (Oct.) 1944.

Altschul reports his observations on the convoluted vessels of the brain and spinal cord. The material, which consisted of normal and pathologic brains and spinal cords, was studied by several methods, but for the most part the modified Van Gieson stain for thick sections and Mallory's connective tissue stain for thin sections were utilized.

In spite of considerable variability in the regional distribution of convoluted vessels, Altschul reports that they are frequently found in the premotor area but are rare in the precentral gyrus. They occur more frequently in the gray-white zone of the insula than in any other part of the central nervous system. They are relatively frequent in the parietal lobe except in the postcentral gyrus, where they are rare. They are not common in the temporal and occipital lobes and are absent in the cornu ammonis and the cerebellar cortex. They are present in the white substance surrounding the dentate nucleus. They are met with rather frequently at the periphery of the thalamus and lenticular nucleus but are rarely found around the caudate nucleus. Relatively many convoluted vessels are found between the white substance of the basis pedunculi and the adjacent substantia nigra, but here their course is less curled than in other areas. They are rarely found in the pons, medulla and inferior olive.

In the spinal cord the convoluted vessels occur in the border zone between the lateral white columns and the gray substance and also in the outer zone of the posterior horn. No statement can be made about a segmental distribution.

In some instances a difference in the rate of growth of the gray and the white matter may explain the form of the convoluted vessels. In others the size of the blood vessels probably influences the occurrence of the tortuosities, because, with the possible exception of some vessels of the spinal cord, the convoluted portion is always found in the arterial segment. In addition to the factor of size, it is possible that some hitherto unknown peculiarities of the mother vessels may be a determining element.

Observations on pathologic material fail to confirm previous observations which indicate that convoluted vessels result from shrinkage of the parenchyma or from the absolute lengthening of the vessel or that they represent parts of newly formed vessels.

In 6 cases of epilepsy convoluted vessels were present in the gray substance proper and were more numerous than under normal conditions. In 1 case they were present in the cornu ammonis. They were not found in 3 other cases of epilepsy, but the small arteries of the pia were convoluted. In 2 cases of Huntington's chorea the convoluted vessels were increased in number and were situated farther inward than in normal brains. However, in 1 case no abnormalities of the convoluted vessels were present.

At this time it is not possible to make a statement as to whether or not there is a causal connection between the convoluted vessels and the clinical symptoms.

GUTTMAN, Philadelphia.

AN INTRACELLULAR BODY IN THE HUMAN CHOROID PLEXUS EPENDYMA AND ITS ANALOG IN THE RETINAL PIGMENT LAYER CELLS OF THE ALBINO RAT. A. E. TAFT, J. Neuropath. & Exper. Neurol. **3**:416 (Oct.) 1944.

Taft describes an intracellular body which can be seen in the ependymal cells of the choroid plexus of man and animals. In appearance it is similar to a body present in the (nonpigmented) pigment cell layer of the albino rabbit eye. In the ependymal cells of the choroid plexus in the Negro, the body itself contains dark brown to black granules, similar in appearance to those seen in the normally pigmented retinal cell layer of the eye.

The cells in these two areas are alike morphologically and present a similar contrast to the nerve cells which lie adjacent to them, the ventricular wall of the brain, and the layer of rods and cones of the eye. They are also similar in their embryologic development.

GUTTMAN, Philadelphia.

Physiology and Biochemistry

MECHANISMS OF OCULAR MOVEMENT IN MAN: INFLUENCE OF THE VESTIBULAR APPARATUS. H. B. PERLMAN and T. J. CASE, Arch. Otolaryng. **40**:457 (Dec.) 1944.

The objective of every movement of the eyes is clear macular vision. This is attained by keeping the foveas opposite the area of interest for a minimal time, about one-fifth second. The most restful or most easily maintained position for the eyes is the central one. In going from one point of fixation to another the eyes always move rapidly. Movement of the eyes may be (1) voluntary (frontal cortex), (2) reflex optic (occipital cortex activated by a retinal image) or (3) reflex vestibular (activated by end organs in the labyrinth). In order that all the demands for movement of the eyes may be met, all three mechanisms must be working normally. Some movements result from a temporary preponderance of the activity of a single center. Other movements represent the associated hyperactivity of several centers.

In the motor area of each frontal lobe there is a center for movement of the eyes which enables one to move the eyes away from the center voluntarily. The ocular muscles are thus voluntarily contracted and overcome the tonic muscle reflexes operating to keep the eyes in the resting midposition. The cortical centers enable the subject not only to move his eyes away from center and keep them there but to make this movement rapidly from one position to another. This can be done under closed lids, that is, without retinal images, or it may be aided by vision—when fixation on a point in one area is rapidly followed by fixation on a point in the new area after the eyes have been moved. With or without retinal images, this voluntary movement is carried out very rapidly, in about one-twentieth second.

Motor fibers that enable the eyes to turn toward an object in the periphery of the visual field, that control fusion, convergence and other activities, originate in the occipital, or visual, cortex. This center is also the source of motor fibers for the ocular muscles concerned with ability of the eyes to follow a moving object. This is not a conscious rapid voluntary movement, like that initiated from the frontal lobe, but a reflex movement, the speed of which is largely controlled by the speed of the moving object and requires retinal stimuli to

sustain it. The retinal images need not be clear. This neural mechanism that makes the eyes follow a moving object can operate even when the occipital cortex is destroyed, presumably through reflex activity at a subcortical level—initiated by moving retinal images. An example of normal cortical function moving the eyes through a small area rapidly and accurately from one point of fixation to another is seen in reading. Here the head may remain motionless, the eyes being moved rapidly to four or six successive points of fixation to obtain retinal images for all the words in one line; then the eyes are moved suddenly and accurately all the way back to the beginning of the next line. Ocular movements may be initiated directly from the frontal cortex or reflexly from the occipital cortex by retinal stimuli. The cerebellum cannot initiate ocular movements but is concerned with the tonus of the extraocular muscles.

The vestibular apparatus is not important for normal movement of the eyes in man. Most normal demands for movement of the eyes can be met by a subject with no vestibular function. Stimulation of the vestibular end organs can, however, initiate movement of the eyes. The fundamental ocular movement resulting from stimulation of the vestibular end organ is slow conjugate deviation away from center; it depends on bending of the hair cells by motion of the cupular substance in which they are embedded. The normal physiologic stimuli for this end organ are movements of acceleration and deceleration. It is a reflex phenomenon, which has a short latent period. The ability to see clearly while moving the head (to move the eye accurately in order to keep it on a point of fixation while the head moves) is perhaps aided by the induced vestibular ocular reflex arising from accurately balanced vestibular mechanisms.

In the presence of spontaneous vestibular nystagmus, more pronounced movements of the eyes are observed when the subject deviates his eyes toward the side of the quick component than when he turns them in the direction of the slow component. This may be explained on the basis of superimposition of vestibular impulses (slow pull) on the tonic impulses tending to move the eye toward center. This results in the cortical stimuli, which operate to maintain deviation, becoming more rapidly inadequate and leads to frequent and more quick movements. When such a person turns his eyes in the direction of the slow component, the eyes can be better maintained in the deviated position, since the vestibular stimulus operating to move the eyes slowly in that direction is now working against the tonic muscle stimuli operating to move the eyes slowly back toward center. Therefore the cortical centers operating to maintain the eyes in the deviated position function more adequately, and the globes are more quietly maintained in that deviated position. If the final common pathways (posterior longitudinal bundle and others) for all ocular movements are affected in the pons, none of the mechanisms for ocular movement may work because of paralysis of the ocular muscles. This may be a unilateral or a bilateral involvement, such as occurs with pressure on or disease of the pons. If unilateral, the unopposed pull of the ocular muscles on the nonparalyzed side may keep the globe deviated away from center and away from the side of the lesion and prevent any kind of movement (voluntary, optokinetic, vestibular) of the globe beyond center toward the side of the lesion. A peripheral lesion of the nerve for the ocular muscle may lead to similar results.

RYAN, M. C., A. U. S.

FURTHER OBSERVATIONS ON THE PRESENCE OF POLIOMYELITIS VIRUS IN THE HUMAN ORO-PHARYNX. HOWARD A. HOWE, DAVID BODIAN and HERBERT A. WENNER, Bull. Johns Hopkins Hosp. **76**:19 (Jan.) 1945.

Howe, Bodian and Wenner report observations on 36 patients who had poliomyelitis. Intracerebral inoculation of rhesus monkeys with inoculum from the oropharynx was employed. The criterion for successful isolation of virus was the production of flaccid paralysis with typical lesions in the spinal cord of the experimental animals, or the production of indubitable lesions alone (1 case).

Virus was recovered from the oropharynx of 10 animals, or 28 per cent. Virus was present in 43 per cent of a series of 23 patients from whom swab specimens were taken during the first three days of the illness. In none of the series of 13 cases in which specimens were obtained after the third day of illness was the virus isolated.

GUTTMAN, Philadelphia.

STUDIES ON SHOCK THERAPY. JUAN NEGRIN JR., J. Nerv. & Ment. Dis. **101**:15 (Jan.) 1945.

Negrin studied the variations produced in cerebrospinal fluid pressure by taking the pressures immediately before and from ten to thirty minutes after electric shock therapy in 3 patients. There was a definite decrease in pressure in 5 of 8 determinations following grand mal convulsions, while no appreciable change was recorded after 3 petit mal episodes. The author suggests that the observations indicate a possible method of studying the correlation of cerebrospinal fluid pressures with venous and arterial pressures.

CHODOFF, Langley Field, Va.

CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDIES: THE ELECTROENCEPHALOGRAM IN PSYCHONEUROTICS. HANS STRAUSS, J. Nerv. & Ment. Dis. **101**:19 (Jan.) 1945.

Strauss studied the electroencephalograms of 100 psychoneurotic patients and compared the patterns obtained with those of 100 control persons. Each record was analyzed for the alpha index, the duration of the runs of alpha activity and the general pattern of electrical activity. In general, the psychoneurotic patients yielded records with less predominance, less continuity and a less amount of alpha activity than were found in the records of the control group. Patients with chronic anxiety and impairment of mental performance were especially apt to have tracings with a small amount and poor quality of alpha activity. With hyperventilation some psychoneurotic patients showed a decrease in the amount and continuity of alpha activity, an observation contrary to the usual increase of or absence of change in this activity.

The fact that alpha activity is decreased in tense psychoneurotic persons can be correlated inversely with the general rule that the amount of alpha waves is increased under conditions of mental and emotional relaxation. Thus, the occurrence of a record showing good quality and continuity of alpha activity in a subject with an apparently severe and chronic psychoneurosis may throw doubt on the depth of the patient's difficulties; conversely, a record showing poor alpha activity in a person suffering from what is apparently only a situational reaction should raise the suspicion of a more

deep-seated emotional disturbance. The improvement in alpha activity seen with hyperventilation in some of the cases indicates that the business of hyperventilation is sufficiently absorbing to push into the background ideas associated with emotional tension. No delta activity with the patient at rest was seen in any of the psychoneurotic subjects studied, and the author feels that delta activity in a patient with alleged psychoneurosis should raise the suspicion of an underlying focal or metabolic disorder.

CHODOFF, Langley Field, Va.

THE CEREBROSPINAL FLUID AFTER ELECTRIC CONVULSIVE THERAPY. JAMES F. MADDUX and C. KNIGHT ALDRICH, J. Nerv. & Ment. Dis. **101**:330 (April) 1945.

Maddux and Aldrich find that there has been little in the literature with regard to changes in the cerebrospinal fluid following electric shock therapy. The authors studied the spinal fluids of 10 young male patients with schizophrenia. The pressure and dynamics of the cerebrospinal fluid were within normal limits on all examinations. The benzidine and Pandy tests gave negative results, and the colloidal gold curve was within normal limits in all cases. The cell count, the total protein content and the levels of sugar in the blood and spinal fluid were likewise always within the normal range. There were no significant differences in the results of examinations made before and after one to ten convulsive treatments.

CHODOFF, Langley Field, Va.

SYNTHESIS OF ACETYLCHOLINE BY TISSUE OF THE CENTRAL NERVOUS SYSTEM. W. FELDBERG, J. Physiol. **103**:367, 1945.

Feldberg has extended previous investigations in which it was shown that acetylcholine is synthesized by slices of brain tissue. It was found that dried and powdered brain substances when suspended in physostigmine-saline solution also synthesized acetylcholine. The synthesis was accelerated by the presence of ether and was depressed, but not consistently abolished, by procedures which interfere with the utilization of oxygen.

The most satisfactory synthesis occurred in suspensions of brain powder in the presence of ether at room temperature. At body temperature the synthesis was accelerated at first but did not continue as long as at room temperature.

Glucose, which accelerates the synthesis by brain slices in appropriate concentration, had no such effect on the synthesis by brain powder. Higher concentrations of glucose inhibit the synthesis in brain slices. The normal blood sugar concentration is inhibitory. Calcium ions inhibited the synthesis in both preparations. Potassium chloride increased the synthesis of acetylcholine by respiring tissue slices and in suspensions of brain powder. The effect in tissue slices was prevented by ether.

THOMAS, Philadelphia.

EXCITABILITY CHANGES AT THE NEURO-MUSCULAR JUNCTION DURING TETANY. STEPHEN W. KUFFLER, J. Physiol. **103**:403, 1945.

Kuffler produced tetany in cats by removing the parathyroid glands and in frogs either by removing the parathyroid glands or by injection of 0.2 to 0.4 cc. of a 2.5 per cent solution of sodium citrate into the dorsal lymph sac. The symptoms were the same regardless of the method used. Particular interest attaches to the results with denervated muscles, which were similar in the two species of animals. The symptoms consisted of fasciculation (synchronous contractions of groups of muscle fibers) and fibrillation (asynchronous twitching of individual muscle fibers). The latter was more frequent and occurred in all preparations. Fasciculation was present in the denervated muscles only during the time required for degeneration of the cut nerve and was attributed to random nerve impulses in the degenerating fibers.

An electric record from the nerve-free end of the fibrillating sartorius muscle showed that the contractions originated in the region of the nerve endings.

The author mentions, but does not describe, experiments which indicate increasing irritability of central synapses during tetany. He concludes that the symptoms of tetany result from lowering of the threshold at the synapses and end plates.

THOMAS, Philadelphia.

FACILITATION, INHIBITION AND DEPRESSION AT THE ARTIFICIAL SYNAPSE FORMED BY THE CUT END OF A MAMMALIAN NERVE. RAGNAR GRANIT and C. R. SKOGLUND, J. Physiol. **103**:435, 1945.

This work extends a previous study in which it was shown that nerve impulses transmitted over efferent fibers in a mixed nerve are relayed to afferent fibers in the same nerve at a region of injury caused by crushing or cutting the nerve. The cut end of the nerve behaves like an artificial synapse. This artificial synapse has many properties characteristic of the natural synapse, for example, synaptic delay and sensitivity to anoxia, fatigue and anesthetics. The author states that in order to behave as an artificial synapse the cut end of the nerve "must be in very good condition." The changes in irritability of the artificial synapse following a conditioning stimulus were studied. There is a refractory period followed by a period of hyperexcitability and in some preparations a series of rhythmic changes in irritability lasting up to twenty microseconds. The artificial synapse manifests dynamic polarity to the extent that transmission is generally better from motor to sensory fibers than in the opposite direction. They also exhibit the phenomena of facilitation and inhibition.

THOMAS, Philadelphia.

Diseases of the Brain

HISTAMINE CEPHALALGIA AND MIGRAINE. LOUIS E. LIEDER, Ann. Int. Med. **20**:752 (May) 1944.

Lieder studied 71 consecutive patients with headache, devoting special attention to the question of allergy. Analysis of the cases showed that 4 patients had histamine cephalalgia, 52 had typical migraine and the remaining 15 had other types of headache, such as so-called hypertensive cephalalgia and anxiety states. Twenty-eight (54 per cent) of the 52 patients with migraine had food allergy. Twenty-three (44 per cent) of the migrainous patients had allergies such as so-called hay fever, urticaria and asthma. A family history of some allergic manifestation or of migraine was obtained from 40 patients (77 per cent). The author concludes that "hypersensitivity plays a major role in causing migraine."

Desensitization with histamine was found to be of value in the successful treatment of patients with histamine cephalalgia. Ergotamine tartrate was recom-

mended for the treatment of migraine, and the use of neostigmine bromide, prophylactically and therapeutically, and inhalation of oxygen were mentioned.

Lieder stresses the fact that the elimination of offending allergens is of utmost importance in the prevention of migraine.

GUTTMAN, Philadelphia.

FOSTER KENNEDY SYNDROME WITH FUSIFORM ANEURYSM OF INTERNAL CAROTID ARTERIES. I. S. TASSMAN, Arch. Ophth. **32**:125 (Aug.) 1944.

Tassman reports the Foster Kennedy syndrome in a case of bilateral fusiform aneurysm of the carotid artery. The patient's only complaints were pain over the right eye and loss of vision in the left eye. The left eye was nearly blind, so that no field was present, and in the right eye there were slight constriction and enlargement of the blindspot. Operation revealed the following: "The left nerve was of normal size and appearance. It was entirely free and not compressed by any visible lesion. Just beneath it was a fusiform aneurysm of the internal carotid artery, which after emerging from the base of the skull formed a complete loop into the region of the sella turcica and then passed backward to its normal location to progress laterally to the middle cerebral artery. It appeared as though the artery was bound to the base of the skull by the ophthalmic artery. On the right side there was a similar fusiform aneurysm, with a mass of tiny veins on it, just beneath the optic nerve. This pressed the optic nerve backward tightly against the posterior edge of the optic foramen. It was impossible to do anything surgically with the lesion. It is believed that ocular difficulty on the left side was caused by sclerosis of the ophthalmic artery, because obviously there was not enough pressure against the optic nerve to cause atrophy and blindness. The pressure against the optic nerve on the right side was definite enough to cause progressive blindness, although one would think there would be atrophy rather than edema of the disk on that side. The pressure, however, may have been just sufficient to cause congestion of the venous blood returning from the orbit."

The paper emphasizes one thing especially—that a number of cases of the Foster Kennedy syndrome with non-neoplastic causes have now been reported.

SPAETH, Philadelphia.

CHRONIC EXTRADURAL ABSCESS IN CHILDREN. JOHN B. PRICE, Arch. Otolaryng. **40**:501 (Dec.) 1944.

Price reports a series of 7 cases of extradural abscess associated with mental deficiency. Six patients were boys ranging from 3 to 13 years of age; the girl was 7 years old. Mastoidectomy was performed because of chronically discharging ears, and extradural abscess was found in all 7 cases, being bilateral in 2 cases. After discovery and treatment of the extradural infection, the children's behavior showed great improvement.

The author believes that the abnormal behavior in the cases reported was the result of pressure from an extradural abscess on the brain. He believes that infections surrounding the brain should always be searched for and all chronically discharging ears should be explored and treated when these conditions are present in mentally backward children.

RYAN, M. C., A. U. S.

THE ENDOCRINE GLANDS IN AMAUROTIC FAMILY IDIOCY. OTTO MARBURG, J. Nerv. & Ment. Dis. **100**:450 (Nov.) 1944.

Prompted by the finding of normal electrical reactions in the asthenic muscles in cases of amaurotic family idiocy, Marburg sought the cause of the asthenia in the endocrine organs. The author studied 3 cases of the disease in children of 1 year 11 months, 3 years and 1½ years in which autopsy was done. In each of the 3 cases there was almost complete absence of adrenal medullary substance and complete lack of chromaffin tissue. This observation is in keeping with the observations in other cases of Tay-Sachs disease with autopsy. On the other hand, the gonadal cells in all 3 cases were prematurely developed, while the interstitial cells of the ovaries and testes were degenerated. Relative hyperplasia of the thymus gland was observed in the cases, together with an appearance indicating functional insufficiency. There was some increase in the colloid of the thyroid, while the hypophysis, parathyroids and pancreas were intact.

The asthenia of amaurotic familial idiocy is thus considered analogous to that seen with Addison's disease and is due to destruction of the adrenal medulla. A similar type of endocrine constellation is found in myasthenia gravis, exophthalmic goiter, amyotonia congenita and possibly familial periodic paralysis. The asthenia in these conditions is presumably due to disturbances in the acetylcholine mechanism.

CHODOFF, Langley Field, Va.

THE PSYCHIATRIC SEQUELAE OF POST-MEASLES ENCEPHALITIS. EDWARD C. SMITH and CARL E. TRAPP, J. Nerv. & Ment. Dis. **100**:555 (Dec.) 1944.

Smith and Trapp report 21 cases of encephalitis following measles studied with regard to the patient's previous history, the neurologic status and the adjustments five and a half years after recovery. All the patients were between the ages of 4 and 12 years, and all were white children. Encephalitis appeared from one to ten days after the diagnosis of measles had been made. Common signs were convulsions, stiff neck, Kernig's sign, coma and paralyses. Complete recovery occurred in from six to thirteen days. In 8 of the cases personality changes followed the encephalitis; these were pronounced in 5 cases. In some cases emotional instability prior to the illness made the degree of damage due to encephalitis difficult to evaluate. In all 8 cases some objective neurologic sequelae, such as hypotonia, strabismus, convulsive state, Babinski's sign, hyperreflexia or pupillary abnormalities, were present.

CHODOFF, Langley Field, Va.

ENCEPHALO-TRIGEMINAL ANGIOMATOSIS. JOHN R. GREEN, J. Neuropath. & Exper. Neurol. **4**:27 (Jan.) 1945.

Green reports a case of a 3 year old boy who had a "port-wine birthmark" over the right frontal and parietal regions, including the area supplied by the first two divisions of the trigeminal nerve on that side. He had frequent and severe left-sided jacksonian seizures, which began after the age of 6 months. In addition, there were left hemiparesis, hemiatrophy of the left side of the body and mental retardation. An area of nonactivity was localized by electroencephalographic study in the right postparietal region. Roentgenograms

of the skull revealed marked asymmetry, the left side being larger than the right. Sinuous, double-contoured calcifications were present in the right anterior parietal region. Pneumoencephalograms showed marked atrophy of the right cerebral hemisphere and moderate dilatation of the right lateral ventricle. Stereoscopic arteriograms revealed increased vascularity and an abnormal tangle of small vessels in the distribution of the middle internal frontal, posterior internal frontal, paracentral and superior parietal branches of the right anterior cerebral artery and of the posterior parietal and central branches of the right middle cerebral artery. There were decreased circulation time through the same vessels, incorporation of the areas of calcification into the terminal distribution of the right superior and posterior parietal arteries on the right side and upward deviation of the terminal portion of the right anterior cerebral artery. Craniotomy was performed, and a hemangioma in the right parietal region was removed. The postoperative course was uneventful; the youngster improved, and the seizures were controlled with phenobarbital.

Green concludes that angiomatosis of the scalp, meninges and brain should be suspected when a child who has a "port-wine mark" in the area of the trigeminal nerve presents convulsions, hemiparesis or mental retardation. The diagnosis is confirmed by the finding of sinuous, double-contoured calcifications in the roentgenograms of the skull. Localization of the pathologic process may be aided by electroencephalographic and pneumoencephalographic studies and, according to Green, should be confirmed by stereoscopic angiograms, especially in cases in which there is no gross calcification.

The characteristic calcifications which occur in the upper layers of the cortex probably represent calcareous degeneration of primary angiomas.

Green, though not unmindful of the contributions of Sturge, Kalisher, Weber, Krabbe and others, suggests that the classification of such conditions preferably be in accordance with descriptive anatomic and pathologic terms because of the variability of the clinical and pathologic pictures. A designation like encephalotrigeminal angiomatosis seems appropriate, rather than a contested combination of proper names.

GUTTMAN, Philadelphia.

CARCINOMA OF THE THYROID GLAND WITH A SOLITARY METASTASIS TO THE SKULL. HOLLIS L. ALBRIGHT, New England J. Med. **230**:573 (May 11) 1944.

Albright reports the case of a 52 year old housewife who had a carcinoma of the thyroid with metastatic lesion in the right frontal region of the skull. Thyroidectomy was performed, followed by partial craniectomy and removal of the metastatic lesion, which had no obvious penetration through the dura. A course of roentgen irradiation was directed to the right temporofrontal region. A follow-up examination two and one-half years after these procedures failed to reveal any evidence of neoplastic disease.

GUTTMAN, Philadelphia.

THE HEALING PROCESS IN WOUNDS OF THE BRAIN. A. H. BAGGENSTOSS, J. W. KERNOHAN, and J. F. DRAPIEWSKI, Proc. Staff Meet., Mayo Clin. **19**:419 (Aug. 9) 1944.

The studies reported by Baggenstoss, Kernohan and Drapiewski were made at necropsy in 70 selected cases in which ventricular puncture had been made for diagnostic purposes. It was found that repair was more vigorous in the cortex than in the white matter. Astrocytes were found to play a minor role in the reparative process, and actual participation of these cells in the formation of a scar was not observed in wounds of less than six months' duration. When repair takes place, the predominant role is played by mesodermal elements —capillaries, endothelium, fibroblasts and leukocytes. Microglia cells appeared to have only a small part in the production of compound granular corpuscles. Most of the latter seemed to have their origin in the endothelial cells associated with capillaries, in the adventitial cells of the larger blood vessels and in the mononuclear cells of the circulating blood.

ALPERS, Philadelphia.

ELECTRIC SHOCK IN THE TREATMENT OF DEMENTIA PARALYTICA. M. C. PETERSEN, Proc. Staff Meet., Mayo Clin. **20**:107 (April 4) 1945.

Petersen reports the results of electrical shock treatment in 34 cases of dementia paralytica. The ages of the patients ranged from 28 to 60 years. The number of shocks administered varied from 2 to 37. Currents of 500 milliamperes applied for 0.2 second were used routinely, but if no convulsion was induced the current was increased to 650 milliamperes. The time of application of the current was increased in a number of instances: 0.3 second in 12 cases, 0.5 second in 9 cases, 0.7 second in 4 cases and 1 second in 1 case.

Of the 34 patients treated, 20 showed great improvement, 9 only slight change and 5 no improvement at all. Four patients showing slight improvement had a relapse, but their condition improved again after a second series of shocks. The best results were obtained in patients of the agitated group.

ALPERS, Philadelphia.

FACTORS IN RECOVERY FROM INJURIES TO THE HEAD. JOSEPH FETTERMAN, War Med. **5**:232 (April) 1944.

Fetterman reviews the many factors which influence the recovery of the patient who has had a head injury. The decisive elements in recovery come under four main headings: the man who is injured, the type of injury, the treatment used and the milieu of the patient.

1. The man who is injured. As a rule the younger the patient the better the prognosis. The personality of the patient, including his intelligence, his dynamic energy and his patterns of behavior, is highly important in all considerations of sickness. Two features of the personality are decisive forces in the reaction of the soldier to injury: his aims and his physiologic reaction to difficulties.

2. The type of injury. The speed and degree of recovery will depend on the pathologic changes. These changes will be influenced by the force of the injury, whether the complication of infection occurs and the site of the damage.

3. The treatment used. Appropriate treatment will include emergency care during the period of shock, measures to provide the optimum conditions for cerebral function, prevention of infection, symptomatic relief and rehabilitation.

4. The milieu. The primary responsibility in treatment belongs to medicine, but the secondary influence of the milieu is considerable. Encouraging contacts, compensation only for organic defects, training and, especially, the chance to be usefully occupied are important helps toward recovery.

PEARSON, Philadelphia.

PROLONGED POST-TRAUMATIC AMNESIA. ADAMS MCCONNELL, Lancet **1**:273 (Feb. 26) 1944.

McConnell reports 6 cases of post-traumatic amnesia prolonged for more than four days after injury. No signs or symptoms were present other than the amnesia, which the author defines as "loss of retention of memory, incapacity to recall recent events, confusion and confabulation." Since other authors have pointed to the ill effects of long-continued traumatic amnesia, McConnell felt justified in breaking the unwritten law that one operates only when hemorrhage is suspected. He made a trephine opening "on each side of the skull, opened the dura" and found subdural fluid in 5 of the 6 cases. This fluid was "blood stained" or "yellow" or "clear." Therefore the condition in these cases was not subdural hematoma, although in a postcript he adds such a true case. Of the 6 patients, 1 died a week after operation of pneumonia, and the rest, including the patient in whom nothing was found at operation, sooner or later recovered. The spinal fluid pressure was never over 135 mm. of water in any of the 6 patients.

The author suggests that the sequence of events was as follows: "Concussion caused a lengthy period of amnesia; during this period a subdural effusion developed, interfered further with cerebral function and so prolonged the existing amnesia." The important practical conclusion is that prolonged post-traumatic amnesia merits subdural exploration.

McCARTER, Boston.

THE CONSTITUTIONAL FACTOR IN ANESTHETIC CONVULSIONS. DENIS WILLIAMS and W. H. SWEET, Lancet **2**:430 (Sept. 30) 1944.

Williams and Sweet studied 42 cases of convulsions occurring during anesthesia and took electroencephalographic records in 22 of them one month to two years after the operation at which the convulsion occurred. Ether was used in 40 cases, divinyl ether in 1 case and pentothal sodium in another. In only 1 case had previous seizures occurred, and in only 1 case was there a family history of convulsions; in 1 case there was migraine, and in 6 of the 22 cases there was a history of "fainting spells." The authors felt that about three fourths of the electroencephalographic tracings were abnormal and that evidence of larval epileptic attacks was seen in one fourth. There was nothing to suggest that the discharges were in any way different from those observed in cases of idiopathic epilepsy or that the seizures themselves differed clinically from typical grand mal.

The authors conclude that convulsions complicating anesthesia are precipitated by any one of a number of factors at the time of operation in patients with an inborn convulsive tendency identical with the tendency assumed to be present in epileptic persons.

McCARTER, Boston.

NEUROLOGICAL COMPLICATIONS OF RELAPSING FEVER. R. B. SCOTT, Lancet **2**:436 (Sept. 30) 1944.

Scott describes 9 cases of relapsing fever with neurologic complications in a series of 41 cases of the disease. Complications were most common after the third week, although they developed at any time. The cases with neurologic complications fell into three classes: those with meningitis, those with focal disease of the nervous system and those with both. The cerebrospinal fluid showed a total protein content of from 60 to 160 mg. per hundred cubic centimeters and pleocytosis, with lymphocytes decidedly predominant.

Treatment with arsphenamine was not helpful. Prognosis was hard to assess. Some patients had repeated relapses, but the majority recovered completely. There were no deaths.

McCARTER, Boston.

SPONTANEOUS CEREBRAL HEMORRHAGE: SURGICAL TREATMENT. ANDRES A. VEPPO, Prensa méd. argent. **31**:1542 (Aug. 9) 1944.

Veppo discusses the possibility of surgical treatment of intracerebral hemorrhage. He reports the case of an 18 year old blacksmith who suddenly began to have contractions of the right side of the face for no evident reason. A generalized seizure with upward deviation of the eyes appeared soon afterward. The next day he had another episode of twitching on the right side of the body, followed by stupor. He was hospitalized and was found to be stuporous, but there were no signs of meningeal irritation. There was generalized hyperreflexia, with a bilateral Babinski sign, normal pupillary reactions, a pulse rate of 72 and a blood pressure of 122 systolic and 84 diastolic. Two days later flaccid paralysis of the right side of the body was noted, but the hyperreflexia continued to be generalized. Lumbar puncture revealed a clear spinal fluid. The fundi showed blurring of the nasal and inferior edges of both optic disks with some engorgement of the veins. There were numerous red cells in the spinal fluid. The Wassermann reactions of the blood and spinal fluid were negative. The patient failed to respond to medical treatment, and an operation was performed eleven days after admission. Ventriculography showed displacement of the ventricular system toward the right. A craniotomy was done, and coagulated blood was removed from the subcortical region after the cortex was incised. The patient showed progressive improvement. Eleven months later he was well except for slight weakness of the right upper limb. Three years after the operation the patient was well, with no recurrence of symptoms. The cause of the intracerebral hemorrhage was not determined by clinical examination.

SAVITSKY, New York.

ACOUSTIC NEURINOMA: COMPLETE EXTRACAPSULAR EXTIRPATION; ANASTOMOSIS OF ACCESSORY SPINAL AND FACIAL NERVES. GERMÁN HUGO DICKMANN, Rev. neurol. de Buenos Aires **9**:239 (July-Sept.) 1944.

Dickmann reports the first case from Argentina in which an acoustic neuroma was extirpated completely by the extracapsular method. A good result was obtained in a 33 year old white woman with the technics described by Dandy and Horrax. An anastomosis between the facial and the spinal accessory nerve was performed eighteen days after extirpation of the tumor, with excellent results.

SAVITSKY, New York.

OCULOGYRIC INSTABILITY AS INITIAL SYMPTOM IN MULTIPLE SCLEROSIS. V. A. JENSEN, Nord. med. (Hospitalstid.) **21**:580 (March 24) 1944.

Jensen reports that oculogyric instability was established in 70 per cent of 50 patients (23 men, 27 women) with multiple sclerosis. It was demonstrable in 12 of the 14 patients with duration of the disorder of a year or less. For examination of the circumductive leading movement the patient is requested to keep his head still and to follow attentively with the eyes an object, such as the end of a fountain pen, shown to him and then made to describe steadily a not too large circle about 50 cm. in front of his face. In patients with multiple sclerosis, even in the initial stage, the circular movement on each side often proceeds in a series of jerks, and an irregular, snappy nystagmus occurs each time the eyes reach one or two definite points in the path of the object. The second phenomenon is bilateral and occurs most often in the upper quadrants of the range of vision, but not in the horizontal line or the vertical meridian.

J. A. M. A.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

HAROLD G. WOLFF, M.D., *Chairman of the Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Dec. 12, 1944

Nerve Regeneration on Vitamin B–Deficient Diets.

DR. CHARLES M. BERRY (by invitation), MR. CHARLES NEUMANN (by invitation) and DR. JOSEPH C. HINSEY.

The tibial, peroneal and saphenous nerves of cats were regenerated normally in the presence of pronounced thiamine deficiency. The rates and quality of the regeneration were determined by observing the return of function and reflexes, which showed a longitudinal growth of the fibers of from 4 to 5 mm. per day. Also, measurements of sweating from the foot pads, records of the action potentials from the excised regenerating nerves and microscopic measurements of the diameter growth of the fibers were made. The regenerating nerves had been crushed earlier with a thin, flat-surfaced forceps only after the cats had shown signs of deficiency on either a carp diet or on a tube-fed diet. The latter contained casein, sugar, corn oil, salts and supplementary vitamins with the exception of thiamine hydrochloride. By injecting small doses of thiamine hydrochloride (20 to 50 micrograms daily), the animals were kept alive as long as one hundred and sixteen days, during which period the nerves were allowed to regenerate.

The cats on the carp diet, which was deficient in thiamine and other components of the vitamin B complex, showed rapid development of anorexia, ataxia and postural disturbances due to damage of the central nervous system, and convulsions. With the better controlled, tube-fed diet the ataxia and convulsions were extremely mild or absent, even in cats which died after periods of up to one hundred and sixteen days. Apparently, damage to the heart produced death in all the cats with thiamine deficiency.

The peripheral nerves, which were excised immediately after the cats died of thiamine deficiency, showed normal action potentials, which demonstrated the ability of all the fiber components in the nerves to conduct impulses. Likewise, microscopic examination showed no damage to peripheral nerves in the thiamine-deficient cats.

DISCUSSION

DR. NORMAN JOLLIFFE: I enjoyed hearing this paper, and in discussing it I have an opportunity to emphasize the difference between acute and chronic lesions associated with deficiency diseases, particularly thiamine deficiency. The acute lesions of thiamine deficiency, whether they are in the pigeon, the dog or the human being, are very similar in that there is no damage to the peripheral nervous system. These animals, and man for that matter, will die of an acute metabolic defect before any damage to the peripheral nerves is evident. Lack of appreciation of this fact led Meiklejohn (*New England J. Med.* **223**:265, 1940) to question seriously whether thiamine is the antineuritic vitamin. It also caused Williams and his associates (Williams, R. D.; Mason, N. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine [Vitamin B_1] Deficiency in Man, *Arch. Int. Med.* **66**:785 [Oct.] 1940), after failing to observe polyneuritis in a group of women maintained on a diet containing about 0.15 mg. of thiamine per thousand calories, to suggest that perhaps thiamine is not the antineuritic vitamin. It was not until these authors placed their patients on a diet containing a larger amount of thiamine that polyneuritis developed. In other words, with a diet very deficient in thiamine the metabolic defect is so prominent as to prevent the development of polyneuritis. Dr. Berry and his associates recognized these facts in their studies, though in their chronic animals the did not produce a true chronic deficiency. For example, in their chronic cats they produced an acute deficiency in about twenty days and then proceeded to give parenterally 20 to 50 micrograms of thiamine hydrochloride, which was sufficient to permit these animals to live forty to one hundred and sixteen days. Such a period is probably too short, especially one of less than ninety days, for a cat to show chronic polyneuritis. In addition, these animals did not present lesions of the peripheral nerves. Such lesions are pathognomonic of chronic thiamine deficiency. A good way to tell whether one has produced chronic lesions of the peripheral nerves in animals is to give a dose of thiamine hydrochloride. If there is prompt response, one is reasonably sure that there is no degeneration of peripheral nerves. If there is no response, anatomic lesions probably are present, and the experimenter will be able to demonstrate them pathologically. I suggest to Dr. Berry and his coworkers that they place their animals on 20 to 50 micrograms of thiamine hydrochloride from the beginning, allow signs of damage to the peripheral nerves, to develop and then give the animals a large dose of thiamine hydrochloride. If the peripheral nerve signs do not respond promptly, the investigators will have suitable animals in which they can study the effect of a chronic deficiency of thiamine on nerve regeneration following injury.

DR. CHARLES M. BERRY: Wintrobe, Follis, Humphreys, Stein and Lauritsen (*J. Nutrition* **28**:283, 1944) found no damage to the nervous system in swine after eight months of thiamine deficiency with a well controlled diet. However, in previous work, Wintrobe and associates (*J. Exper. Med.* **68**:207, 1938) and Kolb and associates (*Tr. Am. Neurol. A.* **67**:189, 1941) produced lesions of the peripheral nerves with diets deficient in compounds of the vitamin B complex other than thiamine.

DR. JOSEPH C. HINSEY: I shall not argue the point with Dr. Jolliffe as to whether we are dealing with an acute, or chronic state. Under the conditions of the experiments as we described them, we found the capacity of the nerve to regenerate to be fairly normal. It seems fairly important that even in the acute state peripheral nerve tissue has the capacity to grow in a fashion which simulates the normal, as nearly as one can study it in normally fed animals. I think that is the point which is of the greatest interest to me in this series of experiments.

PSYCHOSOMATIC PROBLEMS

Genetic and Conditioning Factors in Susceptibility to Disease. DR. GEORGE DRAPER.

Since human disease embraces man as well as his environment, inquiry into the human being's nature is an essential task of the physician. Every effort should be made to study the patient's genetic structure and to observe the modes of response to the inner and outer conditioning factors which effect modifications of the original protoplasmic plan. Three cases are cited as illustrations.

The first, a case of sepsis and pneumonitis due to hemolytic Staphylococcus aureus, was presented to show the direct conflict between a living human organism and invasion from the bacterial field. The patient apparently was cured by sulfonamide compounds and penicillin. How much the man's "will to live," or his emotional attitude, colored the picture could not be estimated.

The second, a case of hermaphroditism, illustrated the powerful influence of xx and xy chromosomes on the faulty establishment of sex. There existed as part of the error a great hypertrophy of the adrenal cortex. A review of this problem led to critical discussion of certain psychoanalytic concepts of sex which refuse to accept the biologic point of view.

In the third case the diagnosis was "anorexia nervosa." Such a term perhaps overemphasized the "purely psychiatric" basis of the patient's difficulty. Observation of the patient from the standpoint of her constitutional status revealed many faults of growth and development. These were interpreted as evidence of genetic faults in the quality of her protoplasm, which during the process of maturing had responded inadequately to the pressure of environment.

The first patient nearly failed in his bacterial contest because of a specialized fault in his forces of immunity. The second, incomplete creature expressed the futile result of specific failure in the organism's biologic phase of sex establishment. The third patient was composed of poor protoplasm, poorly put together. On this basis, physiologic functions generally were limited and unstable in capacity. As part of the total physiologic fault, therefore, emotional disturbances arose.

The discussion was focused on the subject of the whole organism, which is the patient, and, in consequence, on the necessity of properly balanced therapeutic technics appropriate to the full range of medicine.

DISCUSSION

DR. WALSH MCDERMOTT: This paper of Dr. Draper's is in effect a strong plea for the biologic approach to the study of man as an accessory before the fact, or really as a collaborator in the production of human disease.

For centuries men have been studying the soul of man as something rather apart from his body. Particularly during the last three hundred years there has been considerable study of economic man and political man; yet until quite recently the problems of man's inheritances and his struggles as conditioning factors in his diseases have been neglected save for the field of the so-called mental diseases. That this should be so is not surprising when one considers both the immensity of the problem of man's diseases and the lack of notable success up to now in the study of political and of economic man. Hence, one wonders why any one should seriously consider such a study.

Yet there are several reasons that this study must be done. First, as physicians it is our business to treat disease efficiently, and, as Dr. Draper has pointed out, we can approach that efficiency only if we have perception of man's individualities and utilize that perception in modifying our treatment. A more basic reason for the biologic study of man and his diseases is the fact that political man, economic man and diseased man are all the same man, and thus he cannot be trisected or otherwise subdivided. I think it can be assumed that unless the next century or so gives more understanding of that man, specimens of him may be extremely difficult to obtain for study. The field in which this study of man as an accomplice in the production of his diseases is most suitable for biologic study is that of infections. This is despite the fact that, as the bacteriologists lament, there has been no systematic biologic study of the other half of the combination—the infectious agents which cause, or, perhaps it should be said, collaborate with man to produce the disease. Until quite recently, unless a bacterium could ferment wine or kill a man, it received short shrift from the investigators. In a limited sense the term "susceptibility" as applied to an infectious disease indicates whether the infectious agent can gain access to the host. The degree of this susceptibility may vary all the way from complete susceptibility of the host to the opposite extreme. Dr. Draper uses the term "susceptibility," and I agree with him, to cover a larger state, that is, the total reaction of the host to the presence of the infectious agent. In the study of infectious diseases, much work has been done on susceptibility in the limited sense. A great deal of this work was done by Dr. Draper himself; but, as I understand his thesis tonight, he implies that it is not enough, for example, to list whether the incidence of tuberculosis in Eskimos is high or low. Rather, one must study why a particular agent in a particular man produces the particular clinical picture. There are several approaches to this problem of the handling of human infections. One is the approach of some public health officers. Basically, they are interested in man solely as a spreader of disease. For example, they have shown that the incidence of certain infections can be kept within proper bounds by the padlocking of all houses of prostitution, but they have given no thought to the resulting problem of the young man who comes to the city from an area where haystacks abound only to find that in the furnished room, which is all that he can afford, no companions other than men are permitted after dark.

Another instance of the too limited approach to the problem of infection can be seen in the chemotherapeutist who in his zeal for the battle overlooks the battleground. In the treatment of a patient ill with pneumococcic pneumonia and in shock, it is entirely possible to administer enough penicillin to sterilize the blood stream and prevent further extension of the local process in the lungs, only to observe the patient's shock become more profound, with resulting death. I shall wisely refrain from defining the term "shock," as I think Dr. Draper will refrain from a precise definition of "protoplasmic products" and as both Dr. Draper and I would avoid a definition of "democracy"! Yet the point is that once a certain train of physiologic events has been set in motion by the struggle between parasite and host, the elimination of the parasite may not be sufficient to save the host. And there is evidence at present to support the belief that among all the influences which contribute to that state of shock the variability of the individual man may play a role.

One often encounters individual variations in the course of infections because men differ from each other. It so happens that the fat girl in the case described by Dr. Draper did not have an infection, but the phenomenon of the onset of clinical tuberculosis in an obese adolescent who has undergone drastic dieting because of ridicule is a sufficiently common observation. The variation in the reaction of the human host to infection with syphilis is not alone between the extremes of many and of few morphologic changes. In many cases the important disease to the patient is the bare knowledge of the infection itself. Hence, even in the relatively limited field of the infections it is not enough to quarantine the infected man or to destroy the infecting organism; proper attention to the patient himself is essential for proper handling.

As Dr. Draper has presented it, these efforts at adjustment by originally imperfectly balanced and traumatized human beings may become the signs and symptoms of disease. The effort to comprehend these efforts is a real challenge and one, as all here know, which he has not been afraid to accept.

DR. LAWRENCE S. KUBIE: I discuss Dr. Draper's paper with many regrets. I hate to see an honored banner carried in an unworthy cause, particularly when it is held aloft by one who in the past has done so much for a better cause. I regret that I feel it is necessary to criticize unsparingly the doctrine which Dr. Draper has expounded.

Psychosomatic medicine is a search for correlations between the organic agents of disease and the role of psychologic forces in disease. Important correlations of this kind are not to be sought in the rare and the exceptional case. Indeed, if the use of the exceptional case is coupled with the implication that such correlations occur only in extreme cases and that no correlation can be expected with less spectacular ailments, one is likely to be blinded to the subtle interweaving of the organic processes of common diseases and the emotional stresses of everyday life. It takes no great acumen and no special technics to understand that the psychologic development of a child with hypospadias will be different from that of a child with normal genital organs. But it takes an open mind and highly trained technics to explore the correlations between emotional development and such everyday ailments as colds, allergies, troubles with the joints and heart disturbances. Such a correlation goes far beyond a naïve emphasis on body form and its deviations (as illustrated by Dr. Draper's cases). It demands a far subtler appreciation of human personality and physiology.

Therefore, my first point is that the cases which Dr. Draper presents are the freaks in the side show of the medical circus. They are interesting, and they merit scientific investigation for their own sake; but they do not throw light on the fundamental problems of psychosomatic medicine.

As a matter of fact, Dr. Draper overlooks the clinical fact that in appropriate circumstances serious physical handicaps, whether lifelong or acute, may mask neurotic difficulties rather than intensify or expose them. With a broken leg or an acute infection, even persons with frank psychoses may make temporary symptomatic recoveries. This has long been known; and it is one of the strong arguments for the role of emotional factors in such diseases and against the irreversible nature of the changes which underly the psychosis. None of this does Dr. Draper consider.

Furthermore, from what he has said, it would seem that he neglects such considerations because he has failed to grasp the importance of the fundamental concept of "symbolic trauma." He alluded to "symbolic trauma" with a slighting emphasis, which was in itself revealing. He seems to be unaware that the body, its parts and its organs can represent emotional problems and that disturbances in these organs can be a sign language by which the patient attempts to discharge the energies involved in these problems. I shall state without qualification that no one who has failed to grasp this fact understands even the elementary concepts of this important subject.

Indeed, one of these days every physician will think of his patients and their illnesses in terms of symbolic trauma. He will ask himself, "What does this broken leg mean to this man, consciously and unconsciously? What does this rash mean to the patient, consciously and unconsciously? What does this pain or this fever or joint mean on both these levels?" When every physician thinks of disease in this way, then for the first time in human history the physician will have become a mature healer of men. That is why Dr. Draper's slighting reference to the "symbolic trauma" is such an unfortunate and reactionary step.

These, however, are all sins of omission. Dr. Draper is also guilty of sins of commission which are equally serious in that in every reference to psychoanalysis he distorts and misrepresents it. This is of no importance to psychoanalysis; but it is extremely important to medicine, the future progress of which depends in no small part on the wise utilization of analytic knowledge and analytic technic in the study of organic disease. I shall not take the time to dissect and expose all of Dr. Draper's misrepresentations of psychoanalysis. A few illustrations will suffice. Psychoanalysis is usually, although mistakenly, attacked as encouraging licentiousness. Dr. Draper finds it too moralistic. Psychoanalysis is also under attack for being "too biológic," i. e., for neglecting "cultural forces." Dr. Draper finds it to be insufficiently biologic. Actually, both pairs of criticisms are based on ignorance. The theory of libido (or instinct) is nothing else than a theory of the biologic basis of human behavior. It is more than ignorant, however, to lift out of its context a statement, such as the one by Freud which Dr. Draper read. Every one who is acquainted with psychoanalytic literature can cite a dozen places where Freud specifically said that with the gradual increase in understanding of biochemical forces and with the isolation of active biochemical agents the whole analytic process may be shortened. But he always coupled this statement with a warning against premature and naïve efforts to correlate a biology which was still groping with an analytic psychology which was also fluid and formative. Freud's position was always that until both disciplines were mature it was best for each to confine itself to its own technics. Against such cautions no sensible scientist can protest, and in view of so many reiterated statements to this effect it is inexcusable to lift out of its context Freud's statement that in the discussion of sexual behavior he would limit himself to its psychologic aspects and to use that statement as evidence that Freud turned his back on biology.

Finally, lest any one think that this criticism of Dr. Draper's paper grows out of that blind orthodoxy of which psychoanalysts are so often accused, let me state that I have spent the last few years of my scientific life in criticizing psychoanalytic theory and psycho-

analytic technic and in attempting to modify both basically. But, as a constant critic of psychoanalysis, I feel that I have the right to insist that such criticism be based on accurate knowledge and not on ignorance or misrepresentation.

DR. GEORGE DRAPER: I have not much more to say, but it always gives me the greatest satisfaction to have Dr. Kubie take issue. It entertains me to cross swords with so brilliant a student of these problems. This is not the first time that Dr. Kubie has indicated that the selection of too extreme cases is dangerous. If instead of "extreme case" one thinks of an "object of large size," it becomes easier to understand. When one teaches children to read, one first shows them enormous *A*'s, *B*'s and *C*'s, and as they grow older and comprehend the significance of the symbolism of these huge letters they are able to read in small details the significance of these original, enormous, letters. Biology consists of a series of moving protoplasmic patterns which follow simple basic principles, and as the student becomes more and more accustomed to, and understands, these principles he begins to comprehend their significance. Dr. Freud was just a physician, like you and me, at first rather more occupied with chemistry than with medicine, but he was a doctor, a good, kindly man, who became interested in a point of view and decided that his point of view was better than the biologic one. Perhaps it is, but in dealing with life, about which one knows very little, it is important to gather as much information as possible. In the consideration of this whole subject, which has been unfortunately designated "psychosomatic medicine," words have been used with too little thought of their biologic connotation. This dichotomous term does not contain the concept of a living, organismal unit. I remember an old lady saying to me once, "Perhaps you ought not to investigate life; perhaps we are not supposed to know." Of course, intelligent people cannot follow that thesis; biology is an objective study of living nature. Like religion, psychoanalysis is man made, a mental concept, based on a subjective interpretation of what man thinks about life.

Relation of Life Situations, Emotions and Nasal Function. DR. THOMAS H. HOLMES (by invitation), MISS HELEN GOODELL (by invitation) and DR. HAROLD G. WOLFF.

Daily observations on nasal function and structure, including changes in circulation, size of the turbinates, secretion and evidences of obstruction and pain, were made on healthy and on diseased persons. Daily records were also made of the subjects' life situations, attitudes, dominant emotional reactions, effectiveness, energy, fantasies and dreams. Chronologic relationships of the two sets of observations were then formulated. The subjects could be classified as reactors and nonreactors in the sense that the changes in the nose in relation to life situations were far greater and more frequent in some persons than in others.

Although swelling of the turbinates and mucosal vasodilatation often paralleled each other, there was also observed a dissociation of function, in that swollen turbinates were noted with mucosal vasoconstriction. Mucosal edema and pallor sometimes followed prolonged mucosal vasodilatation.

Chilling of the body surface (remote from the nose) was associated with initial mucosal vasoconstriction (pallor), swelling of the turbinates and increased secretion, followed by mucosal vasodilatation, prolonged swelling, increased secretion and obstruction, until the chilling was removed.

Abject fear, dejection and disgust were associated with vasoconstriction, or pallor, of the nasal mucosa, decreased secretion and shrunken turbinates. On the other hand, conflict with anxiety, resentment, frustration, anger and rage were associated with vasodilatation, or redness, of the mucosa, swelling of the turbinates, increased secretion and obstruction. When the latter emotional states were sustained, the associated nasal changes, which were at first usually predominantly unilateral, became bilateral. Also, when swelling and obstruction persisted, pain and tenderness sometimes occurred, spreading over the zygoma and into the temporal region.

In a subject with a large gastric stoma, the circulatory changes in the nasal mucosa in various life situations inducing fear, disgust, anxiety, resentment, anger and frustration paralleled those in the gastric mucosa.

Frank weeping, as well as the feeling of being "on the verge of tears," associated with frustration and resentment was accompanied with pallor and extreme swelling of the nasal mucosa, profuse secretion and obstruction, with complaints of difficulty in breathing. These observations indicate the relation of such sustained swelling, vasodilatation, increased secretion and obstruction with pain to disease of the nose and the paranasal spaces.

DISCUSSION

DR. GERVAIS WARD MCAULIFFE: In my capacity as consultant to the Payne Whitney Clinic during the past twelve years, I have had a rare opportunity to see the close relation between emotional disturbance and function of the nasal structures. Routine examinations of the ears, nose and throat are made on approximately 500 patients a year. To obtain a cross section of this group, I selected at random 50 charts and summarized the observations on the nose, together with the psychiatric diagnoses. Briefly, the data may be summarized as follows:

Of the 50 patients, only 2, or 4 per cent, had an essentially normal nasal condition. Forty-seven, or 94 per cent, had hypertrophy, and injection of the turbinates of varying degrees, and 35, or 70 per cent, had "cloudy" sinuses on transillumination. Twenty-eight, or 56 per cent, had specific complaints referable to the nose. In 35 patients with a condition diagnosed as a psychosis "depression" was a feature. In 12 patients weeping was a persistent and serious symptom, and 3 of these complained that they could not breathe through the nose.

In a large number of patients I have seen in my office the complaints referable to the nose were but one manifestation of their basic problems. For instance, a young married woman aged 26 came to me in March 1944 with a copious watery nasal discharge and the complaint that she could not breathe through her nose. Five years ago she had had similar symptoms in a setting of dissension in her family and the death of a dearly beloved older friend. A submucous resection was done by a competent otolaryngologist. The complaints of March 1944 began in August 1943, in the third month of her second pregnancy, when her husband enlisted in the Navy and was given a deferment from active duty until two weeks after the birth of their child. At the same time her obstetrician told her that she had a weak heart and that she would not be able to take an

anesthetic during labor. Her local physician assured her that her swollen, engorged and dripping turbinates were a feature of her pregnancy and that her discomfort would end with the delivery of her baby. The symptoms continued, however, and grew worse with her loneliness and her unhappy, insecure situation, separated from her husband. She was found to have no special allergies, but she was desperate for relief from her discomfort and confidently expected and hoped for an operation—which I was sure would not solve her difficulties. To make a long story short, in April she found a place to live adjacent to her husband's post on the New England coast, and she is now with him in Boston. Her symptoms began to improve in May, and in her last report to me, at the end of August, she said she was well.

The observations reported by Dr. Wolff and his associates are therefore in keeping with the everyday experience of the otolaryngologist and should stimulate an interest in the broader aspects and implications of nasal disease.

DR. GEORGE DRAPER: Dr. Wolff's discussion has interested me considerably. Five or six years ago a small town practitioner in New England wrote a provocative paper about changes in color of the nasal mucous membrane in relation to emotional disturbances; unfortunately, I have forgotten the reference. Dr. Wolff omitted to state that when the dog-faced baboon becomes emotionally disturbed evidence of that disturbance is reflected in a change in the color of the mucous membrane of the animal's rear end.

DR. OSKAR DIETHELM: I wish merely to draw attention to the fact that this subject was first mentioned by Peyer, who had been influenced greatly by Beard's concept of neurasthenia and the discussion at the gynecologic congress in Washington, D. C. Peyer pointed out that in patients suffering from sexual disturbances due to coitus interruptus he frequently noticed rhinitis. He discussed this relationship in the *Münchener medizinische Wochenschrift* in 1889. I mention this because it shows that these problems have been noted for a long time and were discussed by various authors before Freud's formulation. Another article, by Mackenzie, a nose and throat specialist, appeared in the *Bulletin of the Johns Hopkins Hospital* in 1898. Again, the sexual factor was stressed exclusively. Further literature on this topic can be found in Halban and Seitz's "Biologie und Pathologie des Weibes: Ein Handbuch der Frauenheilkunde und Geburtshilfe" (Berlin, Urban and Schwarzenberg, 1937). Dr. Wolff has presented a much broader aspect of the problem, stressing the importance of emotions. It is interesting to note how little has been published on this topic. Only in recent years has the part which emotion plays in these disturbances of nasal function been brought out, and never as clearly as Dr. Wolff and his associates have done.

DR. GEORGE E. DANIELS: In line with Dr. Diethelm's observation on the literature concerned with the relation of sexual malfunction and the nose, it is of interest to mention some of the work on the association of the nose and hormonal changes. Mortimer, Wright and Collip (Effect of Administration of Estrogenic Hormones on Nasal Mucosa of Monkey, *Canad. M. A. J.* **35**:615, 1936) made observations on 60 pregnant women and found that in 60 per cent of them there was a noticeable swelling of the nose, which increased and reached its height in the ninth month, coincident with the peak of excretion of estrogen in the urine. In observations and experiments on rats in connection with pseudopregnancy, it has been found, among other things, that not only electric stimulation of the head but, in certain instances, the use of a solution of silver nitrate on the nasal mucosa will bring about pseudopregnancy (Shelesnyak, M. C., and Rosen, S.: Naso-Genital Relationship: Induction of Pseudopregnancy in Rats by Nasal Treatment, *Endocrinology* **23**:8, 1939). Dr. Draper has commented on the changes in baboons. It is also of interest that in monkeys with the change in sexual skin which comes at the time of increased sexual stimulation changes have also been noticed in the mucosa of the nose (Mortimer, H.; Wright, R. P., and Collip, J. B.: Effect of Administration of Estrogenic Hormones on Nasal Mucosa of Monkey, *Canada M. A. J.* **35**:503, 1936).

All this shows that the problem of emotional changes in nasal function is a complicated one, and Dr. Wolff and his associates have made extremely valuable observations in regard to this function. Later, when all the data can be considered together and it can be determined to what degree hormonal changes and sexual conflict may enter in, one may come nearer the solution of the problem.

DR. JOHN GALLOWAY LYNN: I want to ask Dr. Wolff about a matter which he did not emphasize in his interesting talk but in which I am especially interested because of its parallel nature to some work I was associated with, that is, the laterality of the effect on the mucous membrane of the nose in 1 of his patients. In this patient, he noted that during euphoria, an almost hypermanic state, the right side of the nose was swollen, congested and red and that when the man's emotional state became normal the nasal condition subsided. I think that with the swelling on the right side the left side was pale. Several years ago, at the McLean Hospital, Waverly, Mass., I noted the same phenomenon of laterality in conjunction with the emotional expression of two sides of the face in a manic patient. He had noticeable hyperactivity of the right side of his face during the manic phase, and during the depressed phase which followed, the emotional expression shifted over to the left side, with a definite blankness on the right side. The shift of symptoms from one side of the nose to the other with the change from euphoria, or hypermania, to the depressed state is interesting, since it parallels the observation of a similar shift in facial expression which I made several years ago.

DR. HAROLD G. WOLFF: As Dr. Lynn pointed out, unilaterality of reaction of the nasal mucosa is a feature. When the reaction is sustained long enough, as for several days, there is a fluctuation of increased redness, swelling and secretion from side to side, but during such a persistent reaction the signs and symptoms on each side increase in magnitude and intensity. This is what we observed in the patient I described. Second, the same man had occasional unilateral migraine headaches on the right side. We have examined his nose during these headaches, and the reaction in the nose was homolateral.

Lastly, as to the relation between sexual function and the nose, I left that out on purpose, because, as Dr. Diethelm points out, the earlier studies dealt with sex as if it were purely an erotic reaction. We have made observations (incomplete as you may guess) on the nose before and during the sex act. There are redness, dilatation, swelling and increased secretion. In the adolescent, in whom masturbation is often coupled with

a sense of guilt, similar reactions occur. I am not at all certain that what one sees in supposedly sexually excited people does not represent as well reactions accompanying conflict and a sense of guilt.

I am grateful to the discussers.

Incidence of Infections of the Upper Respiratory Tract in Relation to Emotional Reactions and Adjustment. DR. J. LOUISE DESPERT (by invitation).

In an attempt to study the psychosomatic factors involved in the incidence of infections of the upper respiratory tract, the records of 63 children (32 boys and 31 girls) admitted to the Payne Whitney Nursery School from 1937 to 1942 were analyzed. The records include anamnestic data, reports on physical examinations and psychometric tests, daily behavior records and records of individual play sessions.

In the process of analyzing the total body of data, it was found that in the group with the highest incidence of respiratory infections there were, besides the 8 children from broken homes, a large number with emotional stresses due to other causes than disruption of the home and a few children who were free from such stresses. Conversely, there were a few children who, while presenting emotional problems, were conspicuously free from colds. There were more boys than girls among the children with the highest incidence of colds. Finally, from the pediatricians' reports it was not possible to differentiate positively between toxic and allergic colds.

Several observations stand out as significant. First, in the total group of 63 children, of equal sex distribution, there were more boys than girls among the children who had more frequent infections of the upper respiratory tract. Second, in the group with the highest frequency there were more children who showed persistence of infantile traits, especially those of an oral aggressive character, and more who had difficulties in adjustment. In this group there were also more children with speech deviations and slightly more in whom bladder training was achieved late. While the number of cases is too small to have statistical value and significance, the psychodynamics in individual cases indicate certain trends.

Saul (*Internat. J. Psycha-Analysis* **19**:451, 1938) reported on 15 patients who came for psychoanalysis because of neurotic symptoms but whose early history showed a high frequency of colds. In 9 of them, colds occurred in "situations of frustration of strong, mostly unconscious, receptive demands with more or less repressed rage."

Studies on stuttering (Despert, J. Louise: *Am. J. Orthopsychiat.* **13**:517 [July] 1943) also bring out the close correlation between repressed hostility and symptoms involving the upper respiratory and upper digestive tracts.

As seen in the group studied, repressed hostility can be manifested in some children by somatic symptoms, of respiratory nature, while in others with similar psychologic factors operating there is total absence of respiratory symptoms and in still others various somatic or neurotic symptoms may be noted. The choice of symptoms involves complex considerations, to a large extent related to the earliest emotional experiences in infancy. Since problems of internal tensions are more common in boys than in girls, it is possible that there is a fundamental sex difference between infants, a difference which may bear in particular on one of the earliest aggressive drives, namely, aggression through the oral zone. Where the aggressive drive is greater, there is more chance for thwarting through training or inadequate mother-infant love relationship. Careful studies of individual and sex differences in infants will offer valuable leads to an understanding of their later adjustment in terms of psychosomatic expression.

DISCUSSION

DR. WILLIAM DOCK: I shall consider only one point in connection with this discussion, assuming for the moment that the data which have been collected really indicate that the children under discussion had more colds. Actually, the data could mean that the parents kept the children home with fewer symptoms. At present I do not believe one can say whether these children were kept home with fewer symptoms than other children or whether actually they had more, or longer-lasting or more severe colds. I should like to point out that in considering the nose the somatic constitution cannot be ignored. Grant and Mudd, who were the first to show that the nasal mucous membrane reacts with the skin, becoming hyperemic when the skin is hyperemic and pale when the skin is pale, found that there are great individual variations. Some people turn red when they are angry, and some people turn pale; and so do their noses. Some people respond strongly and other people very little; this observation has been confirmed in Germany by an otolaryngologist who made studies with a thermocouple on a group of patients, using the same cold stimulus that Grant and Mudd had employed. He found that some persons had pronounced vasoconstriction and others had almost none. Such persons would correspond to the reactors and the nonreactors described by Dr. Wolff. When the patients were questioned by another physician in the clinic who knew nothing of the vasomotor reactions, it was found that the subjects who reacted strongly with vasoconstriction were persons who experienced a great many infections of the upper respiratory tract and that those who did not react had few such infections. This means that if the children from families which had been arbitrarily broken up reacted in this way there must have been an inherited factor which made most of them reactors. In the good old days people were divided into the cold and the dry, the hot and dry, the cold and wet and the hot and wet type; the persons of the type under discussion here are the pituitous people, the cold and wet people, who break up their homes and move around with little consideration for others and who are classically described as having "running noses." The children with "running noses" did not inherit a disturbing situation only; they inherited genes which predispose them to nasal misbehavior.

Dr. Despert's figures show there was a tremendous increase in infections of the respiratory tract in December, January, February and March, with a sharp falling off in April and May, and that in the early months of the fall these illnesses were few. In the early months of the fall the stresses placed on children from their being thrown into the school environment must have been maximal; in spite of that, it was not until the weather became cold that the children had colds. Therefore, these emotional factors must combine with the vasoconstrictor effects of a cold climate to predispose to infection of the upper respiratory tract, and, after all, then only in suitably constituted persons.

If it is found that there is a correlation between these factors, it will have to be concluded that people break up their families largely because they are apt to have children with running noses!

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 23, 1945

GEORGE D. GAMMON, M.D., *Presiding*

Localizing Value of Temporal Crescent Defects in the Visual Fields. DR. H. A. SHENKIN and DR. I. R. LEOPOLD.

This paper was published in full, with discussion, in the August 1945 issue of the ARCHIVES, page 97.

Resection of the Superior Longitudinal Sinus. DR. RUDOLPH JAEGER.

In 1942 I reported 10 cases in which I resected a portion of or ligated the superior longitudinal sinus for the complete removal of parasagittal meningioma (ARCH. NEUROL. & PSYCHIAT. **48:** 977 [Dec.] 1942). In that series I reported the only case in which an unoccluded superior longitudinal sinus was resected at the rolandic inflow of veins; in this case the patient died, although the tumor was tiny. This was the only death in the series, although in 5 of the cases the tumor was much larger, completely occluded the sinus and was situated either at or posterior to the rolandic inflow. From these cases, and from 15 others collected from the literature, it was concluded that resection of the superior longitudinal sinus at any point should not be dangerous provided the vessel already had become occluded by being slowly filled, so that adequate collateral venous circulation had developed.

A fatal case similar to the one in the first series is now recorded. A second surprising case is also reported in which the sinus was ligated back of the rolandic inflow and anterior to the torcular Herophili, where the sinus was not occluded, the favorable outcome indicating that ligation at this point is safe.

CASE 1.—*Resection of meningioma with a portion of the superior longitudinal sinus at the rolandic inflow, with fatal outcome.*

Two years previously a man aged 39 had had a tumor of the left parietal lobe incompletely removed. A second operation was performed on Sept. 25, 1944 because of exacerbation of signs and symptoms referable to the right motor area. A large, boggy, vascular meningioma was isolated from the cortex of the brain. It was a long, bilobed mass, lying tightly against the sinus and apparently infiltrating it. Three weeks later the sinus was uncovered and thoroughly inspected and palpated. It appeared that the tumor was completely occluding the sinus. After the large rolandic veins had been coagulated and severed as they entered the sinus on the right side, about 5 cm. of the sinus and the entire tumor were removed in one mass. The operation was performed without shock, and the patient's condition was good the next day. However, he failed rapidly and died on the fourth postoperative day. Permission for necropsy was not obtained. On opening the resected sinus, it was found that space existed for the passage of blood past the tumor protruding into the lumen.

The fatal outcome in the second case definitely indicates that removal of an unoccluded superior longitudinal sinus cannot be safely performed.

CASE 2.—*Resection of superior longitudinal sinus between the rolandic inflow and the torcular Herophili, with uneventful recovery.*

A man aged 39 presented the complaints of nuchal pain, headache, blurring of vision and general weakness. Examination showed that the patient was somewhat stuporous, with choked disks, left homonymous hemianopsia and weakness of the left arm and the left side of the face. A tumor of the right occipitoparietal region was suspected and an appropriate craniotomy performed. A dense meningioma, weighing 99 Gm., was resected from the sinus midway between the rolandic inflow and the torcular. A portion of it was seen to enter the sinus and was not disturbed. It appeared to occlude the vessel completely.

Eleven weeks later it was decided to remove the involved portion of the sinus with the remaining tumor. A second bone flap was turned over the site of the tumor to expose the sinus adequately. Palpation of the sinus seemed to indicate complete closure of the vessel by a nodular mass. The sinus was tied off above and below the nodule and resected. Examination of the removed specimen revealed that the vessel was still patent, although the tumor filled approximately three fourths of the lumen. Convalescence was uneventful, and the patient has completely recovered except for hemianopsia.

From this case one can conclude that ligation of the superior longitudinal sinus between the rolandic inflow and the torcular Herophili is safe and should be done when a tumor which invades this structure cannot otherwise be removed.

From these 2 cases and the 25 cases previously reported, one may now conclude that the superior longitudinal sinus may be ligated anterior to the rolandic inflow of cortical veins at any point without risk. Ligation at the rolandic inflow can be safely performed only when the sinus has been completely occluded by a tumor. Ligation between the rolandic inflow and the torcular Herophili can be done even though the sinus may still be patent.

DISCUSSION

DR. HENRY T. WYCIS: I should like to ask Dr. Jaeger first whether or not he has ligated the rolandic vein alone without disturbing the superior longitudinal sinus. Second, has Dr. Jaeger conducted any animal experiments with the use of stainless steel plates? Dr. Michael Scott and I have started a series of animal experiments on the repair of defects of the skull with stainless steel plates. This work is unpublished.

DR. WALTER FREEMAN, Washington, D. C.: Has Dr. Jaeger made any arteriographic studies in these cases to determine the condition in the anastomotic veins and in the dural sinuses?

DR. RUDOLPH JAEGER: I have made no angiographic studies in these cases. One might try such a study when a tumor is suspected to involve the sinus, taking the roentgenograms at the venous phase of the injection. This method may be worthy of trial in future cases. Better still might be the injection of a dye directly into the sinus at operation, with roentgenograms taken with a portable machine. This should

show whether or not a nodule is closing the lumen of the sinus.

DR. HENRY SHENKIN: My associates and I have had some experience with cerebral angiograms and second phase venograms at the University Hospital. I do not think that one would be able to see whether the superior longitudinal sinus was thrombosed or not. Often one does not see the vessel at all in presumably normal angiograms.

DR. WALTER FREEMAN, Washington, D. C.: I think that if the roentgenogram is taken late enough one will be able to see it. Dr. Rowe and I presented a paper on arteriography in which that point was emphasized.

DR. FRANCIS M. FORSTER: The section of the brain Dr. Jaeger showed demonstrates well the limits of damage to the cortical gray matter resulting from occlusion of the superior sagittal sinus. It is interesting that pathologically the white matter is not involved by thrombosis or occlusion of either the superior sagittal or the straight sinus, whereas occlusions of both these structures involve the cortical gray matter, the basal ganglia in part and the intervening white matter. This is compatible with Schlesinger's observations on the venous drainage of the white matter.

In regard to Dr. Jaeger's suggested procedure of introducing a small catheter into the superior sagittal sinus to determine whether or not occlusion was complete, I wonder if he has considered the possibility of thus producing an air embolus and if he has considered any methods for circumventing this.

DR. RUDOLPH JAEGER: As far as I can ascertain, the rolandic cortical veins entering the superior longitudinal sinus can be ligated when the situation is normal on one side, as when one is approaching the third ventricle and the pineal recess. When the sinus is ligated, it closes both rolandic inflows and causes certain stagnation of the circulation of both hemispheres in a great part.

With regard to stainless steel plates for closing the skull, I had occasion to remove one of these which I had put in several years before. It was just as bright as when it was inserted. We have used stainless steel wire to close bone flaps many times. It stays bright and shiny, and there is no tissue reaction to it. In opening large veins for any purpose one must be careful not to get air into them. This is the reason I prefer some type of injection of dyes.

As to the question whether one can ligate the superior longitudinal sinus anterior or posterior to the rolandic veins, as nearly as I can make out, it is a safe procedure provided the rolandic veins are not ligated.

The Vasomotor Component of Labyrinthine Vertigo. DR. E. A. SPIEGEL, DR. G. C. HENNY and DR. H. T. WYCIS.

An analysis of the syndrome of vertigo has to take into account not only the disturbances of orientation produced by labyrinthine stimulation but the secondary effects of rhombencephalic vestibulovasomotor reflexes on the cerebrum. In experiments on cats, the cerebral circulation was recorded thermoelectrically on labyrinthine stimulation. With all types of stimulation used (calorization, galvanization, rotation), slowing of the cerebral blood flow accompanied the fall in systemic blood pressure. This reaction, as well as the retardation of the cerebral blood flow on stimulation of centripetal vagal fibers, is chiefly brought about indirectly through the changes in the systemic circulation, since both reactions persisted after interruption of the cervical sympathetic nerve fibers and/or the vasodilator tract joining the facial and the great superficial petrosal nerve. Since impairment or fluctuations of the cerebral circulation may give rise to sensations akin to vertigo, the role played by vascular reactions in the mechanism of labyrinthine vertigo should not be overlooked.

DISCUSSION

DR. GEORGE D. GAMMON: I should like to ask Dr. Spiegel what degree of fall in blood pressure was noted in these experiments and whether vertigo may be the result of fall in systemic blood pressure, with a secondary fall of the cerebral blood flow, or the result of vestibular stimulation. Patients who do not have a sense of directional movement perhaps have only minimal stimulation of their semicircular canals. Is this not also a factor, as well as the fall in blood pressure?

DR. HENRY T. WYCIS: I should like to speak of the technical details involved in this work. In order to dislodge the otoliths from the maculas, it is necessary to rotate the guinea pigs at a rate of 1,000 to 2,000 per minute. Breathing probably ceases during rotation, so that artificial respiration is necessary as soon as the animals are removed from the centrifuge. Another interesting point is the recording of blood pressure in a guinea pig. The carotid artery is cannulated with a fine glass tube, and the animal is heparinized to prevent clotting in the cannula. This is indeed a tedious task and requires skill and patience.

Dr. Spiegel has been the first to show that one can elicit a fall in blood pressure by various methods of labyrinthine stimulation. Furthermore, he has shown that the fall in blood pressure is abolished not by section of the vagus nerve but by section of the cervical portion of the cord.

Some years ago, in an interesting paper, Wotzilka showed that a similar mechanism is present in man. By rotating patients on large tables he was able to show two types of blood pressure reactions. One group of patients showed an initial fall in blood pressure, while the second group presented the same reaction which was demonstrated in the animal experiments, namely, an initial fall followed by a secondary rise.

DR. E. A. SPIEGEL: The fall of the blood pressure is between 10 and 20 mm., similar to the effect produced by stimulation of the depressor fibers of the vagus nerve.

The question whether minimal stimuli may fail to produce ocular reactions but may produce vegetative reactions is a complicated one. I should like to say this: Seasickness or airsickness is certainly a type of stimulation of the labyrinth, since persons with unexcitable labyrinths are immune to motion sickness. Sjöberg had the idea that if one applies fine enough methods of recording one may find some reaction of the eyeballs. That may be possible, but on simple observation one does not note ocular reactions. I think the explanation for this may be sought partly in the following direction: The type of stimulation on shipboard is somewhat different from that in the Bárány chair test. If one rotates the patient in the chair in but one direction, one produces a flow of endolymph and a deviation of the cupola, as has been done in animals, particularly by Steinhausen. Under these conditions one gets ocular reactions. If a person is on a boat and the boat is

rolling for a few degrees to the right and then a few degrees to the left, there is a deviation of the cupola, first in one direction and then in the opposite direction. Hence, the type of stimulation in such a case is rather different from the stimulation on a rotating chair. In the Bárány test one has a deviation of the cupola and, in the example mentioned, an oscillation around the resting point. Thus, there are types of stimulation of the semicircular canals that may produce vegetative, but not ocular, reactions. In up and down movements of a ship, one deals chiefly with otolithic stimulation.

With regard to the role of the splanchnic nerve, I should say that it explains only part of the mechanism. In experiments several years ago, my associates and I made transverse sections of the cervical or the upper thoracic region of the cord; and after these sections we were not able to produce a fall of blood pressure on labyrinthine stimulation. However, when we raised the blood pressure or prevented its fall after section of the cord, the blood pressure was still influenced by labyrinthine stimulation. Probably the reaction of other vascular areas also plays a part in this mechanism.

Book Reviews

Experimental Basis for Neurotic Behavior: Origin and Development of Artificially Produced Disturbances of Behavior in Dogs. Psychosomatic Medicine Monographs. Vol. III. By W. Horsley Gantt, M.D. Price, $4.50. Pp. 210, with 52 illustrations. New York: Paul B. Hoeber, Inc., 1944.

This monograph represents studies on the nervous disturbances of dogs conducted over a twelve year period at the Pavlovian Institute of the Phipps Psychiatric Clinic. The book is sponsored by the American Society for Research in Psychosomatic Problems, Inc.

After a short outline of the Pavlovian concepts and of the methods used in this laboratory, the author proceeds to describe in detail the histories of 3 dogs observed for three, five and twelve years, respectively, and subjected to the same experimental routine. All the dogs showed disturbances in behavior when under stress, but these disturbances were only temporary in 2 of the animals. The third dog did not recover but showed a spread of the disturbance to include other physiologic functions previously not affected and not directly connected with the experimental setting.

The author stresses the existence of "personality" types in dogs which react to stress in a manner dictated by the type itself and which tend to exaggerate the essential characteristics of the reaction. He indicates the possibility of detecting the existence of a conflict by changes in the interrelationship of several conditional reflexes before the overt behavior of the animal becomes disturbed. He shows the reciprocal relation of sexual satisfaction or social contact to its effect in diminishing anxiety. However, a most interesting observation seems to be that the conditional stimulus based on the unconditional reflex connected with food may become pathologic through conflict. It may then be ameliorated, or even abolished, by subsequent association of the same stimulus with another unconditional reflex, such as pain.

In a stimulating chapter, Dr. Ischlondsky gives an analysis of the disturbance in behavior of the dog which was observed for twelve years. While his analysis is based on the Pavlovian viewpoint, a psychologic explanation of the same facts by Dr. Leon J. Saul, based on freudian views, and another by Dr. R. Leighton, from the standpoint of the socioanthropologist, add to the interest and merit of the book. The discussion shows that these explanations are not mutually exclusive and tends further to elucidate various aspects of the experimental data.

The book is highly recommended because the presentation is clear and the material itself is thought provoking. The observations are careful, and their evaluation is scrupulously honest. The book's organization makes frequent repetitions unavoidable, but this does not detract from its interest.

The Care of the Neurosurgical Patient, Before, During and After Operation. By E. Sachs. Price $6. Pp. 260, index and illustrations. St. Louis: C. V. Mosby Company, 1945.

This little book describes the standard technical procedures and equipment used in neurologic surgery at the author's clinic. The general outline of history taking is given, and the details of special procedures, such as lumbar puncture, myelography and ventriculography, are described in detail. The technic of various typical operations is also given. Extremely valuable is the description of some of the finer points in postoperative nursing care.

It is a highly personal book, as befits a publication from the hand of so experienced a surgeon. Electroencephalography is briefly dismissed as a technic in the experimental stage; and while lumbar puncture is mentioned, little guidance is given to the interpretation of results. The Wilkens technic of intradural approach to the gasserian ganglion is advocated. The discussion of the indications for exploration for herniation of the intervertebral disk is refreshingly direct and easily understood.

This is an excellent book for beginners in neurologic surgery.

The Marihuana Problem in the City of New York. Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana. Price, $2.50. Pp. 220, with 33 tables and bibliography. Lancaster, Pa.: Jacques Cattell Press, 1944.

While the smoking of marihuana is rather widespread among the intellectually and emotionally immature population concentrated in the vicinity of Harlem, the Mayor's Committee on Marihuana finds little cause for alarm. The addict knows when he has had enough and refuses an overdose. He does not crave the drug and shows no withdrawal symptoms, relatively little elevation in tolerance, even after a decade of constant use, and little tendency to lapse into severe alcoholism, morphinomania, crime or sexual excesses. The addict employs it for the purpose of enjoying a quiet sociability, with lowered inhibitions and free-ranging philosophic speculations, which are actually on a very superficial level. Mental and emotional deterioration are not demonstrable. This is not to say that there are no toxic properties in marihuana. Acute intoxication can result from overdosage, and psychotic states may follow acute intoxication, but these clear up within a few days.

The Mayor's Committee, made up of outstanding investigators in various fields, has done a notable service in relieving the minds of worried citizens, who were all too likely to take their notions from the Sunday supplements and the rather lurid accounts of the effects of self-administered overdoses by the "romanticists." Clinical studies, superbly controlled, covering medical, neurologic and psychiatric, psychologic, physiologic and sociologic aspects of the problem of marihuana intoxication, are presented in several chapters. The pharmacologic study, by Dr. S. Loewe, is a monograph in itself, opening up a whole new field of compounds (sixty-five) in the class of cannabinols. It makes heavy reading for a psychiatrist, but it points the way toward further studies on possible therapeutic applications. Cannabis indica was dropped from the "Pharmacopeia of the United States" in 1920, but no definite reason is presented for its reintroduction at the present time.

Psychiatry in Modern Warfare. By Edward A. Strecker, M.D., and Kenneth E. Appel, M.D. Price, $1.50. Pp. 88. New York: The Macmillan Company, 1945.

Now that the war is over, one may expect the literature on military neuropsychiatry to turn to efforts to sum up the emotional effects which modern warfare has on civilians and soldiers; to evaluate how the psychiatric problems were recognized and managed, and to be concerned with the inadaptability of some soldiers to return to civilian life. In a sense, then, this little treatise may be considered a forerunner of such a trend.

Though the book is small, its scope is large, and the authors rely on well chosen reports from the literature, reenforced by their personal observations, for the substance of the contents. They lay chief emphasis on predisposition as an etiologic factor in neuropsychiatric conditions. They note no new clinical entity except Mira's "psychorrhexis" in civilians. The psychosomatic developments and the special problems arising from geographic considerations are mentioned.

The trend away from anatomic pathology, prevalent in World War I, toward a more accurate, dynamic psychopathology is evident. The new advances in treatment reflect this advance in the scientific use of narcosynthesis and group therapy.

All this, and many other points, are briefly and clearly presented, making the book easy reading. Its brevity has the disadvantage of slighting points which bear extension; for instance, the program of preventive psychiatry in the armed services, a truly significant advance, rates only a short paragraph.

The section on problems of demobilization stresses the view that every soldier has an adjustment problem and offers advice which boils down to a list of "do's and don'ts," of small educational value.